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Circulation

FICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

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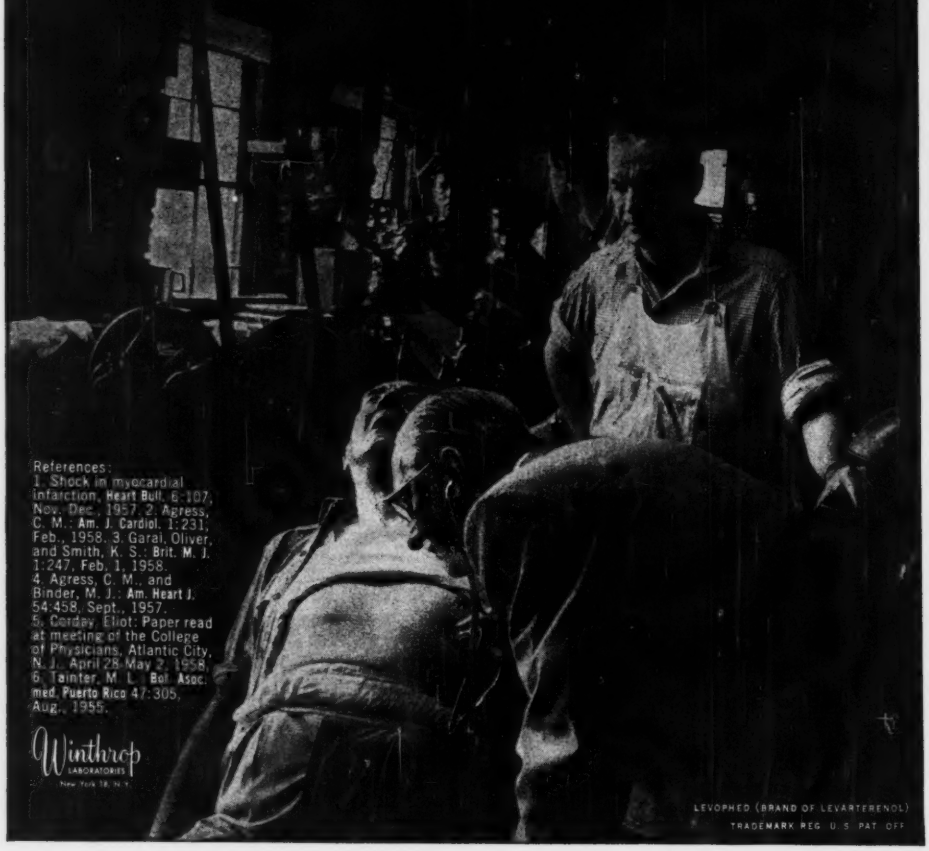

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Editorial

On the Strength of the Heart

KNOWLEDGE of cardiac disease can be divided into its anatomic and its physiologic aspects, both necessary for complete understanding. Nevertheless, clinical interest has at times focused on one almost to the exclusion of the other.

The early point of view is so exquisitely satirized by Molière that I cannot refrain from inserting a short dialogue from "Le Malade Imaginaire,"[1] written in 1673.

The 2 doctors Diafoirus, father and son, enter; the father takes the pulse of "le malade imaginaire" and says,*

"Let's go, Thomas, take the other arm of monsieur to see if you can make a proper interpretation of his pulse."

Thomas. "Dico that the pulse of monsieur is the pulse of a very ill man."

M. Diafoirus. "Good."

Thomas. "That it is somewhat hard, if not actually hard."

M. Diafoirus. "Very good."

Thomas. "Repressed."

M. Diafoirus. "Bene."

Thomas. "And even a little irregular."

M. Diafoirus. "Optime."

Thomas. "All of which indicates an inclemency of the parenchyme splenique, that is to say, of the spleen."

M. Diafoirus. "Very good."

The patient. "No, my other doctor says my liver is sick."

M. Diafoirus. "When one says parenchyme one refers to both."

The printed word fails to convey the beaming smile which spreads over father's face as his son demonstrates so much diagnostic acumen, and the increasing concern of the unhappy patient as he hears these terrifying opinions expressed. Obviously in those early days observations on the pulse loomed large in any clinical investigation.

It was Laennec's introduction of the stethoscope in 1816 that focused attention on the anatomic lesions concerned with the valves, and his followers suggested that cardiac diagnosis was largely a matter of interpreting the sounds heard in terms of valvular lesions.*

The prime importance of this anatomic viewpoint was challenged by James Hope. As early as 1832 he wrote, obviously with mitral stenosis in mind,[2] "symptoms are seldom produced in any very remarkable degree of severity by a mechanical obstacle, unless hypertrophy, dilatation or softening of the heart is superadded."

This more physiologic viewpoint dominated the thinking of the English school for many years. English-trained doctors have told me that their medical school teachers recognized only 2 types of anatomic heart disease, valvular and nonvalvular. This lack of interest in exact anatomic diagnosis was approved by Mackenzie, who questioned whether the introduction of the stethoscope and the consequent emphasis on valvular lesions might not have done more harm than good. Mackenzie's great concern was with the strength of the heart

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*The translation from the French is my own; I have left the Latin words as they are in the original. If my translation does not make very good sense, this is surely what Molière intended.

*I am indebted to Dr. E. H. Holling for much help with the historical introduction I have used. Indeed, the quotations from Hope and Lewis are taken directly from his paper.[3]

and he emphasized the importance of estimating the heart's reserve capacity. Holding much the same views, Sir Thomas Lewis wrote in 1946, "Surgical attempts to relieve cases of mitral stenosis presenting failure by cutting the valve have so far failed to give benefit. I think they will continue to fail, not only because the interference is too drastic, but because the attempt is based upon what, usually, at all events, is an erroneous idea, namely, that the valve is the chief source of trouble."

This was also the prevailing view in America at that time. Though my clinical teachers were much influenced by the German pathologic school, and so interested in the anatomic lesions found at necropsy, Mackenzie's views were highly regarded.

Thus we passed through a long period in which clinical interest in the English-speaking countries was focused on the strength of the heart's beating. When weakened by disease, the therapeutic aim was to restore the heart's strength by rest and by stimulation. Knowledge of structural abnormalities seemed of purely academic interest; what could one do to help them?

The recent successes of the surgeons in mitral stenosis and other conditions have proved wrong both Lewis and a host of other cardiologists. Indeed the possibility of successful surgical attack on other anatomic abnormalities has so greatly stimulated interest in all types of anatomic diagnosis that this field has advanced rapidly. This is common knowledge, but what seems to have escaped attention is that, in the enthusiasm of this advance, the physiologic aspects of heart disease have rather been pushed aside. How many times, dear reader, have you in recent years entered an estimate of the heart's strength into the records of your cardiac cases? Few realize how far the pendulum has swung over, and how completely the anatomic viewpoint has come to dominate cardiologic thinking.

There are several reasons for this decline of interest in the strength of the heart. The advances in the detection of physiologic abnormalities have not been so numerous or so spectacular as those of anatomic diagnosis. The large group interested in the electrocardiogram soon found that, while it yields physiologic information permitting a better understanding of arrhythmias and conduction defects, it gives no information about the strength of the heart. Those using this instrument exhibit great interest in whether an infarct is located anteriorly or posteriorly, but knowledge of the effect of such lesions on the strength of the heart's beating is not to be deduced from that record.

There has always been a group primarily interested in myocardial function, but they have recently concerned themselves chiefly with the estimation of cardiac output and the majority were soon involved in such difficult technics that their efforts have not provided any methods that the ordinary doctor could use.

I am one who objects when the pathologist with the heart in his hand speaks of it as normal. To me it is completely abnormal because it has ceased to beat. The anatomic lesions seen at necropsy do not give information about the strength of the heart during life, for they may or may not influence it. In a large group of conditions—intoxication by certain drugs is only one example—the heart weakens and may cease to beat, but no anatomic lesions are to be found. Indeed this is commonly true in the terminal state of any noncardiac disease. More means are now available to provide information about the heart's strength than most doctors realize. Let us consider what they are.

A theoretical difficulty must be faced first. Though we all know their meaning from experience with our own peripheral muscles, strength and weakness have not yet been expressed in exact terms. As soon as we devise a test, or build apparatus to measure muscular strength or weakness, we find that our results pertain not to the total picture which these words represent, but to some special aspect of it. For the heart muscle, there is the aspect related to the displacement of the blood, the cardiac output; those related to the velocity of the ejected blood, the momentum and the

Newtonian work performed; and that related to the acceleration of blood, the forces developed.[3] In interpreting such data one must not expect any single test to give information on more than one aspect of cardiac strength, and while we will surely need a number of tests to give us the full picture, it is proper to ask ourselves in what direction we should look for a few simple tests to provide us with important information of this kind.

My own thinking on this subject was profoundly influenced by an experience gained when I first simulated systole in cadavers. In the first attempts to mimic cardiac action I pushed in the piston of a syringe attached to a cannula tied into the mouth of the aorta. The muscles of my arm could easily deliver a normal cardiac stroke volume into the aorta against normal arterial pressure, in a normal time. But examination of the records of such artificial systoles disclosed that the pressure pulse contour and the ballistocardiograms were abnormal because I was not accelerating the blood as rapidly as does the normal heart. To meet the challenge and make these records normal required me to deliver not only a normal stroke volume but also a normal acceleration of the blood, and this took more strength than my arm possessed.

Two important concepts emerged from this experience. First, the amount of the cardiac output is no adequate measure of the strength employed in the cardiac contraction; better evidence of strength or weakness is plainly to be sought in what I think of as the higher dynamic functions of the heart, those associated with the velocity and acceleration of the blood. Second, the weakening heart has a resource available to it which has not been emphasized, for, by accelerating the blood less vigorously, a weakened heart can maintain a normal cardiac output and so, despite its handicap, provide the usual blood supply for the tissues. The corollary to this theory is that the earliest sign of cardiac weakness would be revealed by methods which detect changes in the acceleration of the ejected blood.

In any discussion of clinical methods of estimating cardiac function one thinks first of the historic method, the pulse. One wonders if it was in part to improve his ability to detect cardiac weakness in his patients that Mackenzie began to take records of the pulse through the skin. If so, the attempt was unsuccessful for reasons that are now well known. Small differences in the way the pick-up device is placed on the skin over the artery make great differences in the amplitude of the record. Because the pressure necessary to distort the tissues over the artery is so hard to estimate, such records cannot be calibrated accurately in terms of pressure within the vessel. Also the relations between the characteristics of the peripheral pulse and the strength of the cardiac contraction vary with the elasticity of the vessel wall which varies in turn with differences in the blood pressure within it. And obstruction of the lumen at any place between the ventricle and the examining finger does not have to be complete to interfere seriously with the normal relation between pulse and cardiac contraction. So, in my opinion, we are a long way from a satisfactory quantitative method of estimating cardiac function by recording or palpating the pulse through the skin, though obviously the extremes of cardiac weakness and strength can be readily recognized by the examining finger in most cases.

However, if one records the pulse by puncturing a large artery, such as the femoral, much better quantitative work can be done. The more peripheral obstructions are thus avoided. It is well known that vascular elasticity varies with age and there is hope that knowledge of the age alone will permit one to estimate elasticity with an accuracy sufficient for clinical work. Indeed it has been found that after making due allowance for differences in mean blood pressure, the area of the pulse wave correlates well with the stroke volume, the amplitude (the pulse pressure) with the left ventricle's external work, and the steepness of the advancing pulse wave front with the acceleration of the ejected blood.[3] Here then is a way to ascertain this acceleration. But our aim should be a method

that can be frequently repeated, and the necessity for arterial puncture makes frequent repetition impossible. And such a technic has the additional disadvantage that, if pain, apprehension, or discomfort are caused, the body's physiologic reaction may alter the very aspect of cardiac performance that we wish to measure.

Besides these practical difficulties with methods based on the pulse there is a theoretical difficulty which I believe has never been pointed out; indeed I was slow to realize it myself although the facts have long been obvious enough in the results secured in my cadaver experiments. Since the curve of cardiac ejection can be calculated by an adjusted integration of the pulse wave in the root of the aorta,[9] and since this ejection curve is also the second integral of the acceleration imparted to the blood, the pulse is related to the first integral of the forces. It is well known that when one integrates any record the rapid vibrations become less conspicuous; they are, as one says, filtered out. In addition my experiments have provided repeated examples of high-frequency notches and vibrations, very conspicuous in pressure records secured from the root of the aorta, which have disappeared by the time the same pulse wave reached the femoral artery; an old observation, made first, I believe, by Otto Frank. In summary, factors related to the genesis and transmission of the pressure pulse combine to attenuate the record of such aspects of cardiac performance as the forces. If, as I am now prepared to contend, the cardiac forces are of prime importance in any estimate of cardiac function, the pulse as we now record it cannot be expected to provide a first class source of information.

But such theoretical difficulties must not deter us from learning as much as we can from the simple tests that every doctor can make.

Since there is evidence that the amount of the pulse pressure of any beat closely correlates with the external work performed by the contraction of the ventricle which produced it,[5] knowledge of this aspect of cardiac performance can be secured with rough accuracy by a syhygmomanometer. Work is an aspect of cardiac performance related to the velocity of the ejected blood. The pulse pressure should be used for this purpose far more frequently than is done at present, although, like observations of the peripheral pulse, the results will be thrown off by any abnormal obstruction between the ventricle and the site of observation. Also, the error of the auscultatory method is much larger than most doctors suppose. In Ragan and Bordley's data,[10] in which auscultatory measurements were compared with those secured by puncturing the brachial artery, the error of the auscultatory estimate of pulse pressure exceeded 11 mm. Hg in half the estimations and exceeded 22 mm. Hg in 5%.

If we persist in our search for a simple method of detecting the acceleration of the blood, one must turn to the only other instrument which promises to throw light on the problem, the ballistocardiograph. In the form most commonly employed, this instrument records forces, and *force* is *mass times acceleration*. While the simplest instruments of this type are still crude, great progress has been made in getting an undistorted record by more elaborate apparatus.

The H-I segment of the ballistocardiogram, the first part of this record to follow the onset of ejection, reflects the initial cardiac forces very directly. When you fire a gun it kicks you in the shoulder, and one would have no difficulty distinguishing between large and small cartridges by measuring the recoil alone. This simple situation—Newton's third law of motion—is the dominating influence in this early part of the ballistocardiogram. Therefore the slope of the H-I segment gives a reasonably good measure of the initial cardiac forces, those which produce what one might call the jerk of the cardiac contraction.[6, 11] And, as weakness in the motor of your auto is first disclosed by your reduced ability to make a "jack rabbit start" when the light changes from red to green, one has every reason to believe that early weakness of the myocardium would be manifest by a reduced ability to accelerate the blood when systole begins.

As the forces that produce this part of the record are due to motion of blood in the heart and aortic arch[7]—the contribution of blood movement in the right heart and pulmonary artery is only about one fifth as great—obstructions of the arterial lumen distal to this point do not affect this part of the record, though stenosis of the aortic valve would do so. Thus the ballistocardiogram has a definite advantage over observations made on the peripheral vessels, which are so often partly obstructed in older subjects.

When one examines the ballistocardiograms of a large number of patients, looking for evidence of the heart's strength or weakness, the interest seems endless, for abnormality of this type is far more widespread than is anatomic heart disease; many older persons have it, and every dying patient suffers from it before the heart ceases to beat. Of even more importance, cardiac weakness can often be easily and effectively treated, and the same methods that detect it will ascertain the effect of treatment upon it and so help the doctor to discriminate between effective and ineffective measures.

In addition, the analysis of our data secured on patients followed for 20 years now reveals that of the first 100 males thus followed, those with small ballistocardiograms have both died and developed clinical heart disease far more frequently than those with larger records.[8] This is strong evidence that knowledge of the strength of the heart's beating will increase the field of usefulness of the cardiologist, as has so long been believed.

ISAAC STARR

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Editorial

Anatomy and Functional Importance of Intercoronary Arterial Anastomoses

THE development of interarterial coronary anastomoses profoundly influences the clinical course of angina pectoris and acute myocardial infarction and is important in lessening the extent of possible pathologic myocardial changes. The studies by Pitt recorded elsewhere in this issue are a contribution to the problem of the anatomic and functional characteristics of the coronary arterial system that has been debated for centuries. In 1669, Lower[1] stated, "Hence it sometimes happens that, when the lumen of some artery has been too long obstructed or ligated, the blood busies itself in opening a wider channel for its passage in this vessel, must drive and buffet all the more into the next ones, until it has considerably dilated them to give itself room."

Lower did not state, however, whether he had observed interarterial anastomoses between the coronary arteries in the normal heart. In the normal heart, the anatomists have maintained that the coronary arteries are not end arteries.

Proof of their contention is afforded by the observation that a watery solution injected into one coronary artery is immediately seen in all the other cardiac arteries. The physiologists, however, maintain that *functionally* the coronary arteries are end arteries inasmuch as sudden ligation or occlusion of a main stem always produces myocardial infarction.

If a coronary artery is gradually occluded experimentally or by atherosclerotic narrowing, numerous observers have observed the development of functionally important intercoronary communications.[2-7] These anastomotic collateral channels communicate between coronary arteries serving to nourish areas beyond complete occlusions that would otherwise undergo necrosis; others serve as bypasses or detours connecting the artery proximal to the occlusion with the distal portion. Experimentally it has been shown that an animal may survive gradual occlusion of one or more main coronary arteries with little myocardial damage. Indeed, complete occlusion of a main coronary artery gradually accomplished in successive stages often was not accompanied by myocardial infarction in the dog. Similar experimental observations were made by Blum, Schauer, and Calef,[8] by Burchell,[9] by Gregg,[10] and by us.[11] The clinical counterpart of these experiences, i.e., the occurrence of complete coronary artery occlusions without myocardial infarction, has been noted by Saphir and his associates,[12] by Bean,[13] and by ourselves.[4] Recently, however, Snow, Jones, and Daber[14] have questioned the degree to which the collateral vessels protect the myocardium from necrosis. They always found gross myocardial infarction of some extent in association with occlusions, although often considerably smaller than might otherwise have been expected. Since their observations were made in a series of 25 patients, limited to those with clinical manifestations of coronary disease, instances of complete protection from infarction may well have been eliminated from consideration at the outset by the method of selection. In any event there is no question about the development of intercoronary anastomoses in response to obstructive coronary disease and their importance in lessening the consequences of coronary artery occlusion. By the Schlesinger lead-agar or barium-gelatin injection technic, the functionally important collateral channels were

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found to be generally more than 40μ in diameter. Using a wholly different technic of injection of wax spheres, Pitt has reached similar conclusions. Likewise, Baroldi et al.,[15] utilizing a corrosion technic, found increased anastomoses in relation to atherosclerotic occlusions and narrowings.

The hearts of patients with angina pectoris usually show one or more occlusions of the coronary arteries, a rich collateral development, and variable myocardial fibrosis or infarction. While there is a general relationship between the incidence of coronary occlusion and the occurrence of angina pectoris, other modifying factors, such as the exact site of the occlusion, the importance of the vessel involved, the adequacy of the collateral circulation, the rates at which such occlusions or narrowings develop, and the temporary influence of emotion and of vasomotor reflexes, are also of great importance. Although damage to the heart is minimized by the development of the collateral circulation, the margin of safety, or, as it may be termed, "the coronary reserve," is reduced.

In contrast to the general agreement of the findings in the hearts with atherosclerotic narrowings and occlusions, considerable divergence of results has been reported regarding the presence of intercoronary anastomoses in the normal heart. In an extensive series of over 1,500 consecutive normal hearts studied by the Schlesinger technic, the incidence of anastomoses was 9 per cent after exclusion of anemia, cardiac hypertrophy, valvular heart disease, and other categories in which hypoxia evidently leads to an increased incidence of anastomotic development. Although this experience has been confirmed by many others, including the current report by Pitt, in normal hearts Baroldi and co-workers[15] using a corrosion technic, Vastesaeger and collaborators by stereoscopic radiography after injection of Lipiodol,[16] and Laurie and Woods,[17] who used an injection technic, found anastomoses of greater size and with greater frequency. Laurie and Woods, indeed, alone among investigators, observed sizable intercoronary arterial anastomoses in 75 per cent of patients over 4 years of age and in only 23 per cent of patients with severe atherosclerosis. As they state, "much of the difference of opinion has probably arisen due to differences in technique." It is to be hoped that these workers will study a series of cases, observing the precautions and experimental methods found by many other investigators to be reliable, in order to determine whether their exceptional results are due to racial differences in the Bantu, whether the presence of anemia[18–20] in their cases accounts for their results, or whether the differences are due to experimental errors.

Parallel to the anatomic studies described above are the results of the physiologic studies of Wiggers,[7] Gregg, and others[10, 20, 21] that amplify the meaning of the morphologic observations disclosed by the injection technics. An indication of the magnitude of intercoronary collateral development can be demonstrated experimentally by measurement of retrograde flow and pressure from a severed main coronary branch. Immediately following abrupt occlusion of a main coronary branch, the retrograde coronary flow approximates 5 to 5.8 ml. per minute, as compared to control values of 2 to 3 ml. per minute, and is relatively constant in any one dog for a few hours.[10, 21] Measurements of retrograde flow during temporary clamping of the other coronary arteries indicate that these arteries are the major source of flow.

After long-continued obstruction of a coronary artery or a branch in an otherwise normal animal heart, the flow of blood from the cannulated end of the artery becomes quite large. It begins to increase within a few hours, may double within 2 days, and become 3 to 4 times the control level within a week. Within a few weeks, the flows approximate the values for the normal rate of inflow before occlusion in that coronary artery or branch. The observation that the retrograde blood has the same content of oxygen and carbon dioxide as that in a

systemic artery leaves no room for doubt that the collateral circulation is on the arterial side of the coronary capillary bed. The gradual augmentation of retrograde flow is attended by similar elevations of systolic and diastolic pressures in the peripheral end of the occluded coronary artery.

Additional evidence of the functional significance of the collateral vessels is afforded by experimental myographic studies.[7] In the normal dog heart, ligation of a main coronary artery causes the ischemic area to stretch rather than to contract in systole. The intercoronary communications are too small to transfer adequate quantities of blood. Myographic records taken from an area supplied by a slowly occluded artery in dogs indicate that the region is undergoing shortening and that the newly developed collateral channels are functioning in adequate fashion.

Observations of the extent and size of the intercoronary anastomoses in the heart post mortem in man are in accordance with these experimental studies. That the collateral circulation protects the myocardium from damage is generally agreed; a difference of opinion exists only in regard to the degree of protection that is conferred. Available evidence indicates that although sizable intercoronary anastomoses are visible within days after a sudden complete coronary occlusion or sudden narrowing, several weeks are necessary for their rich development and several months may elapse before their full potentiality is realized.

The slow development of these collateral channels emphasizes the importance of rest and reduced activity for many weeks after acute myocardial infarction, contrary to the current tendency to earlier ambulation. Ample evidence exists that reduced cardiac work favors healing of the infarct, reduces the extent of myocardial damage, lessens liability to rupture, and provides time for the development of these anastomotic channels. The slow development of a richer anastomotic circulation is also apparently responsible for the occasional clinical improvement of patients with angina pectoris, the collateral channels acting to offset the narrowing or even the occlusion that has occurred.

HERRMAN L. BLUMGART

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'The knowledge which a man can use is only real knowledge, the only knowledge which has life and growth in it, converts itself into practical power. The rest hangs like dust about the brain or dries like rain-drops off the stones.' (Froude)—William Osler, M.D. *After Twenty-five Years.* Montreal Med. Journal, 1899.

Interarterial Coronary Anastomoses

Occurrence in Normal Hearts and in Certain Pathologic Conditions

By BERTRAM PITT, M.D.

It is generally recognized that interarterial coronary anastomoses of functionally significant size occur with great frequency in the presence of occlusive coronary artery disease and in other conditions such as anemia and cardiac hypertrophy in which myocardial anoxia may be present. Disagreement has been expressed by some investigators regarding the incidence of these anastomoses in normal and abnormal hearts. The problem has therefore been reinvestigated by means of a technic of infusion of saline solution and injection of wax spheres of known size. The results of these observations in 75 hearts are presented and their significance is discussed.

CHANNELS connecting the right and left coronary arteries were first called attention to by Richard Lower of Amsterdam in 1669.[1] The Swiss anatomist Albrecht von Haller demonstrated these anastomoses by dissection of the coronary arteries.[2] The existence of these anastomoses was subsequently denied by Hyrtl,[3] Henle,[4] and Cohnheim,[5] the latter stating that the coronary arteries were true end-arteries. In opposition to the end-artery theory Krause,[6] Langer,[7] West,[8] and others[9–13] again claimed that the coronary arteries communicated through precapillary anastomoses.

It is generally recognized that interarterial coronary anastomoses (greater than 40 μ) occur with great frequency in the presence of occlusive coronary artery disease and its sequelae.[14–19] Anastomoses have also been found in such conditions as hypertrophy of the myocardium,[14, 20] valvular disease,[14] anemia,[14, 21] and emphysema of the lungs.[22] Cardiac hypoxia has been suggested as the common cause of all these conditions.[14]

The important question as to the frequency of occurrence of interarterial coronary anastomoses in normal hearts is however unsettled. Schlesinger et al. using a roentgen-plus dissection method in their investigation of over 1,000 hearts were able to demonstrate interarterial coronary anastomoses (greater than 40 μ) in only 9 per cent of normal hearts.[14, 15] They did, however, assume the presence of abundant fine capillary anastomoses. This is shown by the fact that aqueous solutions injected into one coronary artery are always seen elsewhere in the heart. Their work has been confirmed by Ravin and Greever,[23] and by Maili and Bledsoe[18] using similar methods. A second view is that interarterial coronary anastomoses (larger than 40 μ) are present in a majority of normal hearts. This view is supported by the work of Prinzmetal et al. using an injection method.[19, 24] The same conclusion was reached by Baroldi and Mantero who used a corrosion method,[17] Vastesaeger and Vander-Stratten using a refined stereoscopic x-ray method,[25] and most recently by Laurie and Woods using a modification of the roentgen-plus-dissection method.[26]

On the basis of the work of Schlesinger and Zoll,[14, 15] Beck assumed that only 9 per cent of the normal population have interarterial anastomoses and that the anastomoses resulting from myocardial hypoxia are inadequate for the prevention of infarction. On the further assumption that these channels are an important factor in the fate of patients with coronary artery disease, Beck and others have designed a number of operations to

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increase the collateral circulation of the ischemic heart.[27] It has been said that "the justification for Beck's operation rests on experimental and postmortem evidence that occlusive coronary artery disease cannot promote an effective intercoronary circulation until it is severe."[28]

Since the indication for surgery and the prognosis of occlusive coronary artery disease may be dependent on the presence or absence of interarterial coronary anastomoses (greater than 40 μ) in normal hearts, a reinvestigation of the problem with another method seems justified.

Methods

Seventy-five hearts (table 1) were chosen at random from the autopsy material of the University Pathological Institute. The case material consisted of Swiss Caucasians varying in age from 0 to 90 years. After the investigation for anastomoses a routine pathologic examination was performed.

The heart was removed from the cadaver 5 to 45 hours (average 24 hours) after death and inspected for the presence of rigor mortis. The aorta was then dissected free from the pulmonary artery, and ligatures were placed under the coronary arteries at a point a few millimeters distal to their exit from the sinuses of Valsalva. In adipose hearts it was necessary first to free the coronary arteries from the overlying fatty tissue before placing the ligatures. The aorta was then opened by means of 2 longitudinal cuts that passed within 1 mm. of the valvular ring. A metal catheter was inserted into each of the coronary ostia after which the ligatures were secured. The heart was then suspended from a cross-bar by means of a wire passing through one of the pulmonary veins. A constant pressure flask (fig. 1), adjusted to the appropriate height to exert a maximum pressure of 100 mm. Hg, was then connected to the metal catheters and 100 ml. of physiologic saline were injected into the left coronary artery. If fluid was not seen flowing from the right coronary artery the direction of perfusion was changed and 100 ml. of physiologic saline were injected into the right artery. Once the fluid flowed from the opposite coronary artery a suspension of wax spheres,*[29] 35 to 45 μ and 75 to 90 μ in diameter (fig. 2) was injected into the tubing. Another 100 ml. of fluid were then passed through the coronary arteries at the same pressure, and the fluid that

*The spheres were kindly supplied by Dr. H. Emmenegger, Sandoz Inc., Basel, Switzerland.

Table 1.—*Occurrence of Interarterial Coronary Anastomoses in Normal Hearts and in Certain Pathologic Conditions*

	No. of cases	Age (years)	No. males	No. females	Anastomoses: Present	Anastomoses: Absent
Normal hearts	17	54(0-81)	11	6	3	14
1. History of anemia	2	59(57 61)	2	0	2	0
2. No history of anemia, "normal series"	15	53(0-81)	9	6	1	14
Pathologic hearts	58	69(50-90)	38	20	41	17
1. Occlusive coronary sclerosis* with fibrosis of the myocardium	19	73(50-90)	14	5	17	2
2. Occlusive coronary sclerosis with complete occlusion and infarcton	3	71(55-80)	2	1	3	0
3. Occlusive coronary sclerosis without fibrosis or infarction	5	69(50-79)	3	2	1	4
4. Fibrosis of the myocardium without occlusive coronary sclerosis	17	68(51-83)	12	5	14	3
5. Infarction without occlusive coronary sclerosis	1	82(82)	0	1	0	1
6. Valvular lesion plus hypertrophy	7	62(49-79)	3	4	3	4
7. Hypertensive heart disease plus hypertrophy	6	65(54-79)	4	2	3	3

*Occlusive coronary sclerosis refers to those cases in which the coronary arteries were found to be markedly narrowed.

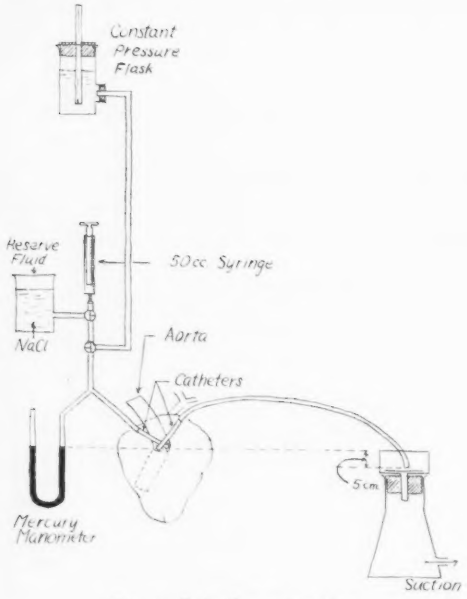

FIG. 1. Injection apparatus.

came out of the artery was collected on a filter. This filter lay in a funnel that had been inserted into a suction bottle. The difference in height of the coronary ostia and that of the free end of the tubing suspended over the suction flask was 5 cm. The filter paper was then removed from the suction flask and examined microscopically. The presence of spheres was considered evidence for the occurrence of interarterial coronary anastomoses. The investigation was completed in 15 minutes, so that this method could be used in conjunction with the routine autopsy. In contrast to other methods, the heart remains intact for further pathologic examination.

A disadvantage to this method is that the anastomoses cannot be localized. The possibility also exists that anastomoses may not be demonstrated even if present. This would apply particularly when one of the main branches of a coronary artery is occluded proximal to its collateral channel. The suspension of spheres could then pass from the patent artery through the anastomoses but could not leave through the occluded ostium. Another technical problem is that perfusate escaping from the vascular bed can enter the myocardium, and simulate infarction. This necessitated the histologic confirmation of all suspected infarcts.

RESULTS

Results are shown in table 1. Anastomoses were found in only 6 per cent (1 out of 15) of the hearts in the "normal series." In those cases with occlusive coronary artery disease, and fibrosis of the myocardium or infarction, anastomoses were found in 75 to 100 per cent of the cases. With occlusive coronary disease but without fibrosis or infarction, anastomoses were found in 25 per cent of the cases. In hypertensive heart disease and in hearts with valvular lesions, anastomoses were demonstrated in 43 to 50 per cent of the cases.

Of the 3 cases of normal hearts with anastomoses 2 were not included in the "normal series," since anemia (hemoglobin 70 per cent or less)[14, 21] is known to be a factor in the production of anastomoses. The other patient with anastomoses in a normal heart had a history of epileptic attacks for the past 9 years. The inclusion of this case in the "normal series" may also be questioned, since epilepsy can produce hypoxemic changes.[30]

No relationship could be found between the age at time of death or sex and the presence of absence of anastomoses.

DISCUSSION

Anastomoses were found in only 6 per cent of normal hearts but could be readily demonstrated in many pathologic hearts especially with occlusive coronary artery disease and fibrosis of the myocardium. These results are in agreement with those of Schlesinger, Blumgart, Zoll and others using the roentgen-plus-dissection method.[14, 15, 18, 23]

It is interesting that our results do not agree with those of Prinzmetal,[19, 24] who used a similar injection method. A comparison of the 2 methods discloses some factors that could account for the differences of results. 1. In the present study the hearts were examined on an average of 24 hours post mortem at a temperature of 22 C., whereas Prinzmetal injected the hearts after keeping them for 24 hours at 4 C. and 4 hours at 37 C. 2. We used wax spheres (fig. 2) (35 to 45 and 75 to 90 μ) in a perfusate of physiologic saline, whereas Prinzmetal used glass spheres of varying diameters (40 to 200 μ) in a perfusate with a viscosity close to that of blood. The glass spheres used by Prinzmetal have

been shown to have jagged and sharp spicules.[31] 3. We used a maximum pressure of 100 mm. Hg both for perfusion and injection, whereas Prinzmetal used a pressure of 200 mm. Hg for perfusion and 160 mm. Hg for injection.

It is unlikely that the first 2 factors are mainly responsible for the differences in results. Although the author examined the hearts for the absence of rigor mortis, there may have been some residual vascular spasm remaining in the smaller vessels; but this cannot account for the finding of anastomoses only in the pathologic hearts. The second and third factors, perfusion and injection pressure in conjunction with the sharp spicules on the spheres, perhaps account for the difference in results. Wiggers has stated that a pressure of 100 mm. Hg is slightly higher than should be used.[32] The pressure in an occluded coronary artery is not that of 0 but 20 to 30 mm. Hg during diastole and 40 to 50 mm. Hg during systole. The difference between the pressures in the functioning and in the occluded coronary artery is therefore less than would be expected and is perhaps within the range of 60 to 80 mm. Hg. We have therefore used a pressure of 65 mm. Hg for both perfusion and injection and found it to be adequate in many cases. Baroldi et al.[17] and Vastesaeger et al.[25] have also used excessively high pressures for injection. Although Schlesinger et al.[14, 15] have used pressures up to 200 mm. Hg, they were able to demonstrate anastomoses in only 9 per cent of normal hearts. This can perhaps be explained by their use of a perfusate that did not penetrate uniformly to vessels smaller than 40 μ. The walls of the smaller arterioles and capillaries were therefore not subjected to the high pressures. An adequate explanation of Laurie's and Woods'[26] finding of frequent anastomoses in normal hearts, with use of a slight modification of Schlesinger's method must await further study. It is therefore possible with a pressure of 200 mm. Hg that the anastomoses demonstrated with such frequency by Prinzmetal and associates[19, 24] are the result of stretching pre-existing capillary channels and of creating artificial communications.

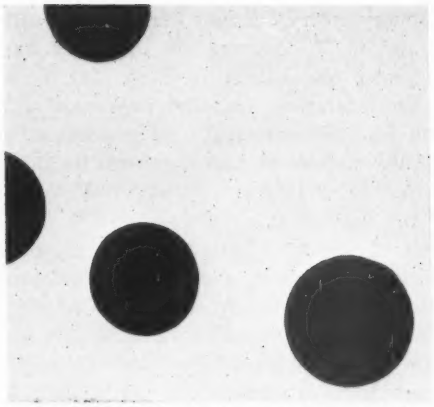

FIG. 2. Spheres 75 to 90 μ, 100 $\times$ enlarged.

It is probable that the anastomoses (greater than 40 μ) found in hearts with occlusive coronary artery disease are functional in many instances and that coronary arteries are not physiologic end-arteries as suggested by Porter in 1896.[9] This view is supported by the experimental work of Kolster[10] and by many observed cases that have complete occlusion of a coronary artery without evidence of ischemia or infarction.[33–35] Further evidence is that infarction may occur in an area whose primary vessel is patent but whose collateral supply is occluded ("infarction at a distance").[15, 36, 37] In normal hearts the abundant capillary network connecting the coronary arteries cannot be expected to serve as a functional collateral blood supply because of the high resistance across these channels.[9] If there are interarterial anastomoses in normal hearts (greater than 40 μ), no substantial evidence of their function has as yet been presented. Spalteholz and Hirsch showed experimentally that the size of an infarcted area is smaller than that of the area supplied by the obstructed vessel.[12, 38] Prinzmetal used this observation to justify the presence of anastomoses in normal hearts, stating, "the degree of collateral circulation in the (normal) heart is not sufficient to prevent an infarction following obstruction to a major

coronary artery but may limit the size of the infarction."[19] Wiggers, on the other hand, suggested that it is more likely that the size of the infarction is smaller because of diffusion from the surrounding myocardium.[32] It has also been shown that the size of the infarct cannot be correlated with survival or death of the individual after infarction.[39] On the basis of present evidence the functional significance of these anastomoses in normal hearts, even if present, is uncertain.

Although the present results support those who advocate procedures for establishing prophylactic anastomoses in normal hearts, a certain amount of caution is in order. Beck has applied his operations mainly to patients with angina pectoris or previous myocardial infarction.[40] It has been adequately shown that these are the very people who have an anastomotic circulation. It can be argued that the anastomotic circulation is inadequate for the needs of the myocardium and that additional help afforded by the operation might give the heart sufficient reserve to relieve angina pectoris or to prevent infarction. The evaluation of whether the actual increase in anastomoses or whether psychologic factors are responsible for the results obtained by Beck and others will have to await careful follow-up of patients and controlled studies.

Summary

A method is presented for the study of interarterial coronary anastomoses. Wax spheres (35 to 45 and 75 to 90 μ) were injected into one coronary artery at a maximum pressure of 100 mm. Hg. The finding of spheres in the opposite coronary artery was considered positive evidence for the presence of anastomoses.

A total of 75 hearts randomly selected were studied with this method. Of the 15 normal hearts only 1 (6 per cent) was found to have anastomoses. In those cases with occlusive coronary artery disease, fibrosis of the myocardium and infarction anastomoses were found in 75 to 100 per cent of the cases. In hypertensive heart disease and in hearts with valvular lesions, anastomoses were demonstrated in 43 to 50 per cent of the cases.

These results are in agreement with those of Schlesinger, Blumgart, and Zoll, who used the roentgen-plus-dissection method but are in disagreement with the finding of anastomoses (greater than 40 μ) in the majority of normal hearts by Prinzmetal by means of an injection technic similar to the one used in this study.

The factors accounting for the difference in results between this study and others are discussed.

Acknowledgment

The author wishes to express his gratitude and appreciation for the constant help and encouragement of Dr. W. Schweizer, Department of Medicine, University of Basel, and to thank Professors Werthemann and Scheidegger, Pathological Institute of Basel, for the generous use of the autopsy material and the pathologic diagnoses.

Summario in Interlingua

Es presentate un methodo pro le studio de anastomoses inter arterias coronari. Spheras de cera (con diametros de 35 a 45 e de 75 a 90 μ) esseva injicite in un arteria coronari sub un pression maximal de 100 mm de Hg. Le constatation del presentia de spheras de cera in le opposite arteria coronari esseva considerate como prova positive pro le existentia de un anastomose.

Un total de 75 cordes, seligite per randomisation, esseva studiate per medio de iste methodo. Inter le 15 cordes normal includite in le serie, anastomose esseva constatate in solmente 1 caso (6 pro cento). In le gruppos de cordes con morbo occlusive de arteria coronari, con fibrosis del myocardio, e con infarcimento, anastomoses esseva constatate in inter 75 e 100 pro cento del casos. In casos de hypertensive morbo cardiac e incordes con lesiones valvular, anastomoses esseva presente con un frequentia de inter 43 e 50 pro cento.

Iste resultatos es de accordo con le constatationes de Schlesinger, Blumgart, e Zoll, qui laborava con un methodo a roentgenographia e dissection, sed illos non concorda con le constatation de Prinzmetal quie reporta le pre-

sentia de anastomose (de plus que 40 μ) in le majoritate del cordes normal super le base de investigationes con un technica injectional simile al technica usate in le presente studio.

Es discutite le factores que pote explicar le differentia inter le resultatos del presente studio e illos de studios per altere autores.

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Neither is it true which is commonly believ'd, that the heart by any motion or distention of its own doth draw blood into the ventricles, but that whilst it is moved and bended, the blood is thrust forth, and when it is relax'd and falls, the blood is received in manner as follows.—William Harvey. *De Motu Cordis*, 1628.

Paradoxical Results of Infundibular Resection in Tetralogy of Fallot

By E. M. M. Besterman, M.A., M.D., M.R.C.P.,
T. V. O'Donnell, M.B., M.R.C.P., M.R.A.C.P., and
Walter Somerville, M.D., F.R.C.P.

The ultimate aim of surgical treatment of Fallot's tetralogy is complete anatomic repair by removal of the obstruction to pulmonary blood flow and closure of the ventricular septal defect. This ideal has been achieved by a small number of surgeons using a pump oxygenator and cardiac arrest. Until it can be realized by all, less complete operations will be performed that will improve the condition without correcting it. Considerable clinical improvement follows infundibular resection by open cardiotomy with or without pulmonary valvotomy. Paradoxically some of these patients may develop a syndrome of heart failure due to the development of a left-to-right shunt through the ventricular septal defect.

THE 7 patients discussed in this paper had severe disability due to Fallot's tetralogy. By means of hypothermia infundibular resection and pulmonary valvotomy were carried out under direct vision in 5 patients and infundibular resection alone in the other 2. Except for 1 instance, the operations were successful in that the disability and cyanosis virtually disappeared. At the same time, however, all the patients developed signs of cardiac failure, namely a raised venous pressure and cardiac and hepatic enlargement. The purpose of this paper is to explain how these seemingly paradoxical results came about.

There were 7 patients in this series, 2 male and 5 female (table 1). Five of them were aged 6 to 13 and the other 2 were 17 and 26 years. The diagnosis of Fallot's tetralogy had been confirmed by angiocardiography. A Blalock-Taussig operation had been performed on 4 of them 4 to 8 years previously; in 2 of these patients, the operation was repeated on the opposite side. All these operations had been unsuccessful; from the absence of the characteristic murmur, the anastomosis was considered to have closed in all except 1 child who retained a faint continuous murmur. All were cyanotic at rest and showed clubbing of fingers and toes. They became a deeper blue and very breathless after a quick walk of 50 yards or less.

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Methods

The operations were performed by Mr. Holmes Sellors under hypothermia at 30 C.[1] After the circulation had been occluded, a small incision was made into the right ventricular outflow tract. The infundibular stenosis was resected by knife, scissors, or punch on the anterior and lateral aspects so that the obstruction between the ventricle proper and the infundibulum was relieved.

Five of the 7 patients had valvular stenosis in addition to the infundibular obstruction. Here the incision in the ventricle was prolonged upwards or a separate incision was made in the anterior wall of the pulmonary artery. The valve, which was cone-shaped, was divided in 2 places from the narrowed orifice toward the valve ring so as to leave an adequate channel.

In the course of the ventriculotomy the ventricular septal defect was well visualized in 2 cases (J.B. and S.S.). Two or 3 sutures were inserted, and the defect appeared to be closed completely in J.B. and partially in S.S. Postoperative catheterization however showed that the defect remained patent in both patients.

Clinical Course

After 6 to 12 months, all 7 patients admitted to little or no disability and were not restricting themselves in any way. Five of them showed no trace of cyanosis at rest (arterial oxygen satura-

TABLE 1.—*Features before and after Operation**

Patient	Sex	Age	Age at previous Blalock operation	Cyanosis	Clubbing	Disability	Systolic murmur (length)	Hemoglobin (per cent)	Heart size (CTR)	Valve (V) or infundibular (I) stenosis	Pulmonary diastolic murmur
Pre.	F	10		4	4	3	2	147	44		0
J.B.			5							I	
Post.				0	1	0	4	87	58		0
Pre.	F	13		4	3	3	3	144	52		0
R.G.			5 & 9							I	
Post.				0	1	1	4	87	63		+
Pre.	F	7		2	2	3	3	101	50		0
S.G.			—							I.V.	
Post.				1	0	1	4	87	57		+
Pre.	F	6		4	4	4	2	160	39		0
J.R.			—							I.V.	
Post.				0	0	0	4	88	58		+
Pre.	M	7		2	2	2	3	107	42		0
S.S.			—							I.V.	
Post.				0	1	1	3	87	60		+
Pre.	M	26		4	4	3	3	165	48		0
L.S.			18							I.V.	
Post.				0	0	1	4	98	57		+
Pre.	F	17		4	4	3	2	164	49		0
D.W.			9 & 11							I.V.	
Post.				0	0	0	3	97	58		+

*Grading is from 1 (the least) to 4 (the most).

tion 95 per cent or over). Two had slight cyanosis (85 and 88 per cent saturation). The patients were not observed after strenuous effort, but they or their parents said that their color did not change after exercise. The hemoglobin content of the blood returned to normal in all cases (table 1).

The following features of the early postoperative course were common to all patients: cyanosis was replaced by a pink skin color, the jugular venous pressure rose to the level of the angle of the jaw with the patient at 45°, and radiologically the heart size and pulmonary vascular markings increased (fig. 1 and table 1). In the patient J.R., the clinical and radiologic picture of left ventricular failure and pulmonary edema followed the development of right ventricular failure after 1 week but responded promptly to digitalis, mersalyl, and sodium restriction.

On auscultation (fig. 2) a long systolic murmur loudest in the third left interspace replaced the short pulmonary systolic murmur; a pulmonary diastolic murmur appeared in all but 1 patient, and pulmonary valve closure (P_2) became audible in 2 patients with infundibular stenosis only. The murmur appeared to extend through systole and it continued up to or past aortic valve closure (A_2), which was audible but ended before P_2, which was either faint or inaudible.

In the electrocardiogram (fig. 3), the signs of right ventricular hypertrophy changed to right bundle-branch block in 2 cases with T inversion extending as far as V_5 1 year after operation. Inverted T waves in the chest leads were the only changes after 1 year in 2 cases, and in the remainder, the tracings were unaltered.

Cardiac catheterization demonstrated a left-to-right shunt at ventricular level in all patients. A small right-to-left shunt remained in 2. The degree of shunt is reflected by the ratio of pulmonary to systemic flow: this was 2 to 1 or more in 4 of the 7 patients. The pulmonary systolic pressure was 40 to 65 mm. Hg in 5 cases, but the pulmonary resistance was less than 4 units (320 dynes sec. cm.$^{-5}$) in all. The right ventricular diastolic pressure was significantly raised in 3 cases and the right atrial pressure was high in 6 cases with a dominant "a" wave. "Wedge" pulmonary capillary pressure was raised in the 3 patients in whom it was recorded. The catheterization data are detailed in table 2.

DISCUSSION

In Fallot's tetralogy, the right ventricle pumps a considerable amount of its output into the aorta where the resistance is lower

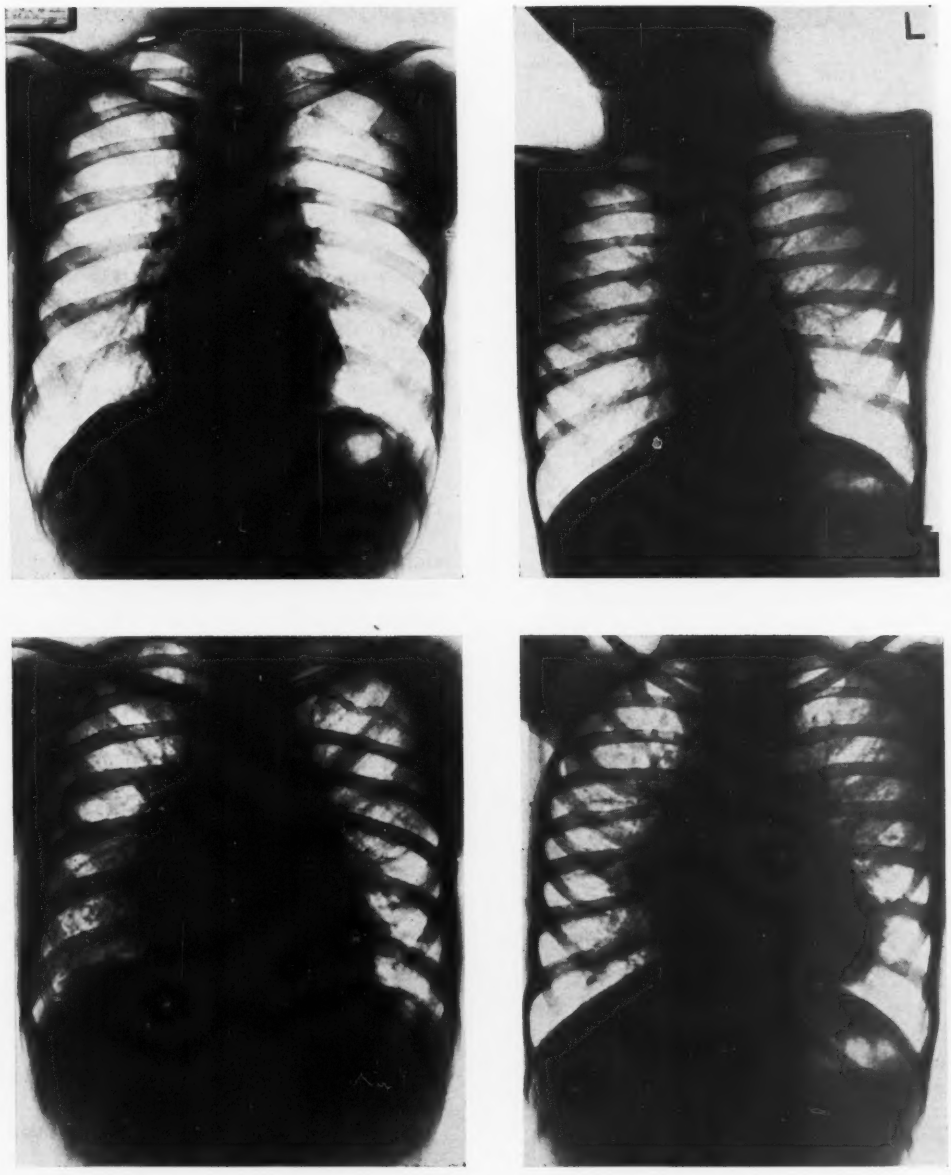

FIG. 1. Chest x-rays before (*above*) and after (*below*) operation. The heart size has increased and pulmonary plethora has developed. *Left.* Male, L.S., age 26. Cardio-thoracic ratio before operation 48; 1 year later, 57. *Right.* Female, J.R., age 6. Cardio-thoracic ratio before operation 39; 9 months later, 58.

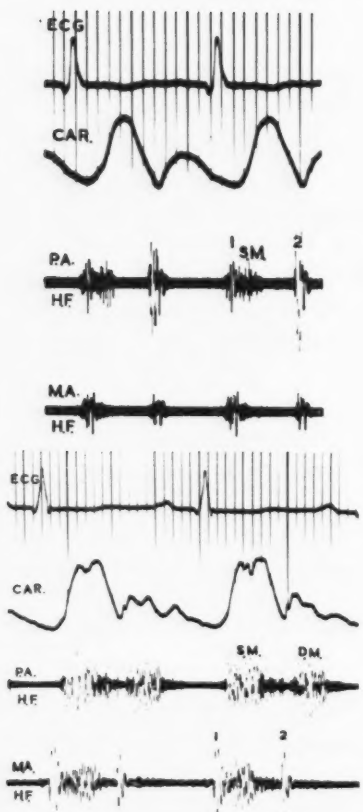

FIG. 2. *Top.* Phonocardiogram to illustrate typical features of severe Fallot's tetralogy: short pulmonary systolic murmur (*SM*) of ejection type, single second sound (*2*) due to aortic valve closure, P_2 is not present. *Middle.* Postoperative phonocardiogram showing prolonged pulmonary systolic murmur (*SM*) and diastolic murmur (*DM*). *Bottom.* Postoperative phonocardiogram showing prolonged pulmonary systolic murmur (*SM*) and both aortic (A_2) and pulmonary valve closure (P_2), the latter of low amplitude. Pulmonary incompetence is not present. *CAR.*, carotid arterial pulse; *H.F.*, high frequency; *M.F.*, medium frequency; *M.A.*, mitral area; *P.A.*, pulmonary area; *1* and *2*, first and second heart sounds.

than that due to the infundibular or pulmonary valve stenosis. Brock[2] first advocated the removal of the obstruction to the right ventricular output so that the pulmonary blood flow would increase and the amount of blood shunted into the aorta would be reduced or abolished. The object of removing the infundibular or valve obstruction under direct vision in the present cases was to achieve such a redirection of flow. This has occurred but other, perhaps less desirable, sequelae have resulted, similar to those described in a single case by McCord and Blount.[3]

Interventricular Shunt. Although the pressure in both ventricles remained identical in 5 of the 7 patients catheterized after operation, the shunt from right ventricle to aorta disappeared in all except 2 and in these cases it was greatly reduced. However, a left-to-right shunt developed in all 7 patients. The radiologic appearance of pulmonary plethora and of cardiac enlargement were the first signs of this shunt, and it was subsequently confirmed by catheterization. The redirection of blood flow resulted from the removal of the obstruction to the pulmonary flow. The pulmonary vascular resistance was consequently lower than the systemic and the left-to-right shunt developed. The increase of heart size may be partially attributed to the rapid onset of this shunt. Wood[4] has suggested that the disproportionate degree of right ventricular enlargement results from the need for the right ventricle to pump a greater volume at systemic pressure. This increase in right ventricular work was followed in all cases by the development of right ventricular failure within 3 days of operation. The clinical rise of jugular venous pres-

ure reflected the rise of mean right atrial ressure and a dominant "a" wave was due o the increased resistance to filling of the entricle. Radiologic enlargement of the trium also occurred.

Pulmonary Circulation. The pulmonary irculation was suddenly exposed to a greatly ncreased blood flow. The normal pulmonary asculature could accept such an increase with little or no rise in pressure but in Fallot's tetralogy, the pulmonary vessels are abnormal and a two- to four-fold increase in pulmonary systolic pressure resulted from an increase in flow 1½ to 5 times the normal (table 2). Pulmonary capillary venous pressures were recorded in only 3 patients. In 2 children, these values were a little above normal (8 and 13 mm. Hg) and in the third, a man aged 25, there was a considerable increase (28, 22, 25, and 19 mm. Hg for "a," "x," "v," and "y" respectively). The total pulmonary resistance did not exceed 4 units (or 320 dynes sec. cm.$^{-5}$) in any case, and the pulmonary arteriolar resistance was considerably less. The Eisenmenger syndrome was not seen to develop. It would seem that the pressure increase was the result of several factors: transmission of the high right ventricular systolic pressure, increased pulmonary blood flow, raised left atrial pressure, and limitation of distensibility of the pulmonary arterioles.

Pulmonary incompetence was created at operation in 6 of the 7 cases, including 1 with normal pulmonary valves. Keith[5] proposed that the competence of the pulmonary valves depended on the support of the ventricular muscle that extends to the valve ring, a view confirmed experimentally by Brock.[6] Although the valvotomy in the present cases was designed to produce a competent valve as far as possible, regurgitation resulted, partly because the newly fashioned flaps failed as a valve, and partly because the supporting musculature of the valve ring had been damaged.

The hemodynamic effect of pulmonary incompetence in this situation is difficult to assess. While it would appear to add further to the right ventricular stroke volume, it is probably of lesser importance. This point is illustrated by case J.B. in whom considerable

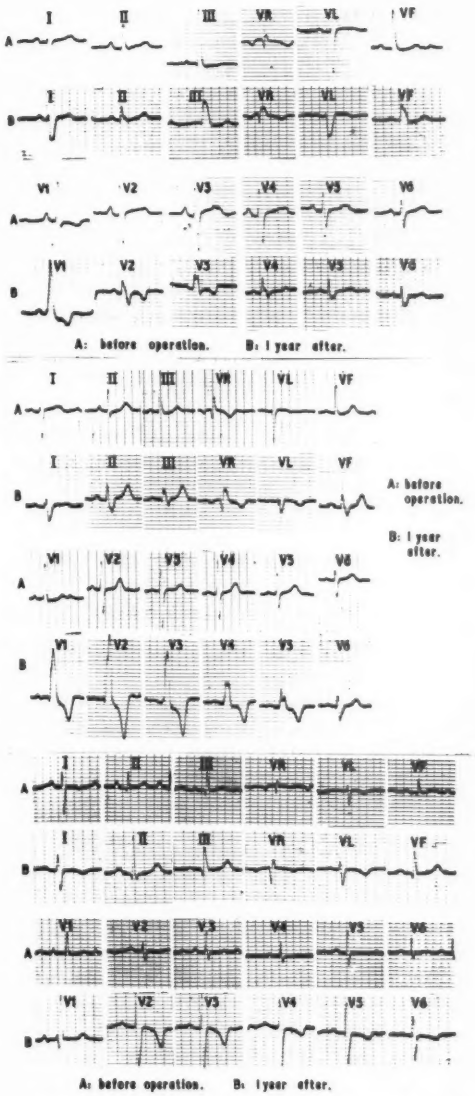

FIG. 3. Preoperative electrocardiograms are typical of Fallot's tetralogy. After operation, right bundle-branch block developed and was present after 1 year (*upper* and *middle*). T inversion in the chest leads is a prominent change in all 3 graphs.

TABLE 2.—*Postoperative Cardiac Catheterization*

Name	SVC* Sat. (%)	RA Press.†	RA Sat. (%)	RV Press.	RV Sat. (%)	PA Press.	PA Sat. (%)	PCV Pressure†	Syst. art. Press.	Syst. art. Sat. (%)	Blood Flow Pul. (L./min.)	Blood Flow Syst. (L./min.)	Interval after operation
J.B.	63	6 —1 +1 0	63	80/ 6	71	N.E.	N.E.		75/ 0	95	3.0	2.3	6 mo.
R.G.	62	5 —5 0 —2	68	90/ 0	78	65/15	85		100/65	96	10.4	3.3	11 mo.
S.G.	61	15 3 10 4	61	75/10	74	40/10	72	7 4 16 5	75/44 A	85	same		7 week
J.R.	61	7 —2 2 0	59	96/ 2	87	64/ 6	89	mean 13	96/40	96	12.5	2.7	13 mo.
S.S.	60	12 0 9 0	60	90/15	69	50/10	70		90/50 Cuff	96	1.3:1		3 mo.
L.S.	50	19 4 14 7	51	110/20	65	60/12	77	28 22 25 19	110/65	88	6.0	2.8	2 mo.
D.W.	67	2/0	69	100/ 0	79	25/ 2	76		125/62	96	5.7	3.0	8 mo.

*SVC, superior vena cava; RA, right atrium; RV, right ventricle; PA, pulmonary artery; PCV, pulmonary capillary venous area; Syst. Art., systemic artery; Pul., pulmonary blood flow; Sys., systemic blood flow.

†Levels of atrial waves, a, x, v, and y. All pressures in millimeters of mercury.

postoperative cardiac enlargement developed in the absence of clinical pulmonary incompetence. Furthermore, pulmonary incompetence after successful valvotomy for pure pulmonary stenosis is fairly common. Blount et al.[7] have observed 3 such patients for 3½ years without noting any ill effects. The evidence from animals with intact septa is equivocal; when the pulmonary valve is completely excised in dogs, heart failure does not follow at rest, but right ventricular hypertrophy always develops.[8] Diminution or regression of the pulmonary incompetence has not been noted in the present cases over a period of a year, as far as can be judged from auscultation or phonocardiography.

Left Ventricular Function. In Fallot's tetralogy, the presence of a longstanding right-to-left shunt and an underdeveloped left ventricle may appear incompatible. It should be remembered, however, that the upper margin of the ventricular septal defect is closely related to the dextroposed aortic root. Consequently the shunt traverses only a small part of the left ventricular outflow tract and the body of the ventricle bears no extra load.

There appear to be 2 possible causes of left

entricular failure in these cases. The first s transmission of the raised right ventricular liastolic pressure to the left ventricle when ight ventricular failure appears. The left itrial pressure would then rise as it did in 3 of our patients in whom it was measured. The second is the inability of the underdeveloped left ventricle to deal with the increased pulmonary venous return consequent on the newly acquired left-to-right interventricular shunt. It is impossible to be sure which of these 2 factors is principally responsible for initiating left ventricular failure. It seems likely that both play a part and are closely interrelated.

This syndrome is not peculiar to Fallot's tetralogy after infundibular resection, for it has been observed after a Blalock or Pott's anastomosis. The extent to which it develops after infundibular resection depends on how freely the stenosis is removed. Partial resection, leaving a large systolic gradient between pulmonary artery and right ventricle, is often followed by great improvement, but an inadequate resection may be fatal. These results are presented as only an intermediate step in the complete anatomic correction of Fallot's tetralogy, the final one being the closure of the ventricular septal defect. In the first 2 patients in this series, Mr. Holmes Sellors attempted to close the defect after dealing with the stenosis, but the time available with hypothermic circulatory occlusion was too short and the defects were only partially closed. The future policy is to complete the correction when an efficient bypass is available. It is not clear at present whether Fallot's tetralogy is best treated by excision of the stenosis and closure of the ventricular septal defect in 2 stages as envisaged here, or in 1 stage as reported by Lillehei and his coworkers.[9] Although the former course has been followed *faute de mieux*, it would appear to have the advantage of allowing the right ventricular outflow tract and pulmonary vasculature to become adjusted to an increased flow while an emergency escape valve remains in the form of the ventricular septal defect.

Summary

After a more or less complete excision of the infundibular stenosis, with or without pulmonary valvotomy in 7 patients with Fallot's tetralogy, a syndrome emerged with the following features:

Immediate changes: the disappearance of cyanosis, signs of right heart failure with cardiac enlargement, radiologic and, in 1 case, clinical evidence of left heart failure, increase in the duration and intensity of the systolic murmur, appearance of a pulmonary diastolic murmur, increased pulmonary blood flow.

Subsequent changes: regression of clubbing, improved effort tolerance, continued elevation of jugular venous pressure. The possible mechanism of these changes is discussed.

Summario in Interlingua

Post le excision plus o minus complete del stenosis infundibular (con o sin valvotomia pulmonar) in 7 patients con tetralogia de Fallot, un syndrome se manifestava con le sequente characteristicas:

Alterationes immediate. Disparition de cyanose, signos de disfallimento dextero-cardiac con allargamento del corde, indicios radiologic (in 1 caso) clinic de disfallimento sinistro-cardiac, augmento del intensitate e del duration del murmure systolic, apparition de un murmure pulmono-diastolic, e augmento del fluxo de sanguine pulmonar.

Alterationes subsequente. Regression del phenomeno de digitos hippocratic, meliorate toleration de effortio, e continuate elevation del pression in le venas jugular.

Le mechanismo possibile de iste alterationes es discutite.

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The credit of pointing out the analogy between this condition and angina pectoris, which is ascribed usually to Potain (1870), but which is maintained by Weber to be due to Brodie (1846), belongs in reality to Allan Burns, whose Observations on Some of the Most Frequent and Important Diseases of the Heart (1809) is a well-known storehouse of interesting facts. Since, so far as I know, this distinguished writer's connection with this supposed new theory has not been pointed out (except in the second edition of my Practice), I will read to you in full what he says on the subject: "Such a state of the arteries of the heart (referring to atheroma) must impair the function of that organ. It has been long known, that although the heart is always full of blood, yet it can not appropriate to its own wants a single particle of fluid contained in its cavities. On the contrary, like every other part, it has peculiar vessels set apart for its nourishment. In health, when we excite the muscular system to more energetic action than usual, we increase the circulation in every part, so that to support this increased action the heart and every other part has its power augmented. If, however, we call into vigorous action a limb round which we have with a moderate degree of tightness applied a ligature, we find that then the member can only support its action for a very short time, for now its supply of energy and its expenditure do not balance each other; consequently, it soon, from a deficiency of nervous influence and arterial blood, fails and sinks into a state of quiescence. A heart, the coronary vessels of which are cartilaginous or ossified, is in nearly a similar condition; it can, like the limb begirt with a moderately tight ligature, discharge its functions so long as its action is moderate and equal. Increase, however, the action of the whole body, and along with the rest that of the heart, and you will soon see exemplified the truth of what has been said, with this difference, that as there is no interruption to the action of the cardiac nerves, the heart will be able to hold out a little longer than the limb.

"If a person walks fast, ascends a steep, or mounts a pair of stairs, the circulation in a state of health is hurried, and the heart is felt beating more frequently against the ribs than usual. If, however, a person, with the nutrient arteries of the heart diseased in such a way as to impede the progress of the blood along them, attempt to do the same, he finds that the heart is sooner fatigued than the other parts are, which remain healthy. When, therefore, the coronary arteries are ossified, every agent capable of increasing the action of the heart, such as exercise, passion, and ardent spirits, must be a source of danger."—William Osler, M.D. *Lectures on Angina Pectoris and Allied States*, 1897.

The Electrocardiographic Pentalogy of Pulmonary Emphysema

A Correlation of Roentgenographic Findings and Pulmonary Function Studies

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With the Technical Assistance of C. J. Lloyd and H. Bauers, B.A.

The clinical applicability of the routine electrocardiogram and the chest roentgenogram in assessing advanced pulmonary emphysema is shown by a correlative study on 150 adults with moderately severe and severe pulmonary emphysema determined by pulmonary function studies. From these data a rather uniform electrocardiographic pattern has emerged entitled "the electrocardiographic pentalogy of pulmonary emphysema" which by itself suggests the presence of an advanced emphysematous state.

A previous publication[1] established the presence of exaggerated P waves and resultant T-a wave inscription in leads II, III, and aV_F of the adult electrocardiogram in patients with severe emphysema. Continued focus upon the electrocardiogram of patients with advanced pulmonary emphysema has resulted in the identification of an electrocardiographic pattern which, by itself, suggests the presence of an advanced emphysematous state. This pattern will be referred to as the "electrocardiographic pentalogy of pulmonary emphysema;" it consists of (1) exaggerated P waves in leads II, III, and aV_F, (2) prominent T-a waves in leads II, III, and aV_F, (3) vertical cardiac position, which at times may be extreme, (4) clockwise rotation on the longitudinal cardiac axis, and (5) tendency to low voltage, particularly in the left ventricular leads V_4 to V_7.

The present report is concerned with the electrocardiographic analysis of 150 adults with moderately severe and severe pulmonary emphysema, selected solely on the basis of tests of pulmonary function and the correlation of roentgenographic interpretation of pulmonary emphysema with the pulmonary function data.

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MATERIALS AND METHODS

One hundred and fifty emphysematous adult patients were selected for study on whom 1 or more routine electrocardiograms and chest roentgenograms were available. All patients had moderately severe or severe pulmonary emphysema as established by pulmonary function tests.[2] The arbitrary classification based on alteration of function is shown on table 1.

The routine 12-lead electrocardiogram was classified into 6 groups according to the presenting pattern, namely, (1) the electrocardiographic pentalogy of pulmonary emphysema, as previously outlined, (2) the partial pentalogy, in which the degree of clockwise rotation and low voltage across the left precordium was less marked, (3) absent T-a-wave patterns, with marked degrees of vertical position, clockwise rotation, and low voltage, (4) the pattern of the short P-R interval and depressed RST segment, with vertical cardiac position, variable degrees of clockwise rotation, and left ventricular low voltage, which has previously been described,[1] (5) instances of right ventricular preponderance, patterns of right ventricular dilatation and patterns of right bundle-branch block, and (6) essentially normal electrocardiograms. Included in groups I and II are 9 instances of unusual cardiac axis presentation that superficially suggest left axis deviation but, in fact, are expressions of severe vertical position.

Posteroanterior roentgenograms were available on all patients, the majority having lateral films as

TABLE 1.—*Arbitrary Classification of Pulmonary Emphysema Based on Alterations of Pulmonary Function*

Classification of emphysema	2-second vital capacity (%)	Maximum breathing capacity* (%)	Single-breath O_2 test (%)
Moderately severe emphysema	45 - 70	45 - 70	4 - 8N_2
Severe emphysema	<45	<45	>8N_2

*All patients had elevation of their spirogram to the hyperinflation level denoted by circled E.

well. They were classified as normal, or as showing minimal, moderate, moderately severe or severe emphysema by gradation of the following criteria:

Signs Due to Increase in Thoracic Volume. Depression and flattening of diaphragm; increased anteroposterior thoracic diameter often associated with increased dorsal kyphosis; elevation of the sternum with increase in angulation between manubrium and body; widening of the intercostal spaces.

Signs Due to Alterations in Pulmonary Parenchyma. General increase in radiolucency of lung fields along with local emphysematous bleb and bulla formation, usually at the bases or apices; superior retrosternal radiolucency increased in lateral projection; increase in interstitial markings resulting from increased contrast between hyperaerated alveoli and supporting structures (interstitial fibrosis is also a factor in some cases).

Cardiovascular Changes. Decrease in peripheral vascular markings per unit area; vertical cardiac position; enlargement of pulmonary artery in severe emphysema.

Although the films were on a select group of patients, the observer was unaware of the clinical state or laboratory data, and these films were intermixed with films of nonemphysematous patients. Fifty films of the study group were subsequently re-read to check the accuracy of recording.

Of the 150 patients in the present study, there were 71 and 79 instances of moderately severe and severe emphysema, respectively. The average age for the entire group was 57 years, with a range from 23 to 78 years. Cardiac position and cardiac rates were determined on all electrocardiograms. T-a waves of 1 mm. or more in leads II, III, and aV_F were required for inclusion in groups I and II.

RESULTS

The incidence of the various patterns, the degree of presenting emphysema, and the roentgen findings in the 6 groups are shown in table 2.

The results are considered according t individual electrocardiographic patterns.

Pentalogy Pattern. The typical electrocar diographic findings are exemplified in figur 1. Thirty-four of the 51 patients in this cat gory had severe pulmonary emphysema o pulmonary function tests, and 36 of the 5 x-rays were interpreted as showing mode ately severe to severe emphysema, with additional roentgen interpretations of mode ate emphysema.

Partial Pentalogy Pattern. The range c this pattern is shown in figure 2. The an plitude of the left precordial potentials wa consistently less than 8 mm. The moderatel severe and severe emphysematous groupin was equal on function testing. Roentgeno graphically, 14 of the 30 patients had mod erately severe to severe emphysema, with 9 additional instances of moderate emphysema.

Absent T-a-Wave Pattern. Save for the lack of P-wave and T-a-wave augmentation, the over-all electrocardiographic tracing simulated that of group I (fig. 3). The T-a waves were either less than 1 mm. or were absent. There were approximately equal numbers of moderately severe and severe emphysema on function testing, with 8 instances of moderately severe to severe emphysema and 6 instances of moderate emphysema identified on roentgen examination. Conversely, 6 x-rays were interpreted as normal or showing minimal emphysema. Single instances of atrial fibrillation and an ectopic atrial pacemaker accounted for 2 of the failures of T-a-wave inscription in this group.

Short PR Interval-Depressed RST Segment. This interesting pattern is responsible for marked RST segment depression in leads II III, and aV_F, due to the T-a-wave expression distal to the QRS complex. The P-R interval i usually 0.12 second or less in duration. Although 6 of the 9 patients had severe emphysema, the roentgenograms were interpreted as moderately severe to severe emphysema in only 4.

Right Ventricular Preponderance, Dilatation, and Right Bundle-Branch Block Contrary to previous reports in the literature

TABLE 2.—*Incidence of Presenting Electrocardiographic Patterns, Degree of Pulmonary Emphysema and Roentgen Findings in 150 Patients with Moderately Severe and Severe Emphysema*

ectrocardiographic classification	No. of patients		Moderately severe emphysema on pulmonary function tests						Severe emphysema on pulmonary function tests					
				Degree of emphysema identified on chest roentgenograms						Degree of emphysema identified on chest roentgenograms				
	Total	% of total	No. of patients	None	Min.	Mod.	Mod. severe	Severe	No. of patients	None	Min.	Mod.	Mod. severe	Severe
ntalogy	51	34	17	0	4	5	5	3	34	0	2	4	14	14
rtial pentalogy	30	20	15	1	6	3	5	0	15	0	0	6	7	2
bsent T-a wave	20	14	9	1	3	3	2	0	11	1	1	3	3	3
ort PR interval-depressed RST segment	9	6	3	1	1	1	0	0	6	0	2	0	1	3
ight vent. preponderance, dilatation, and right bundle-branch block	8	5	2	0	1	1	0	0	6	0	2	1	1	2
Normal electrocardiogram	32	21	25	4	13	6	2	0	7	1	4	1	0	1
Totals	150	100	71	7	28	19	14	3	79	2	11	15	26	25

these 3 patterns were in a distinct minority in the current study. There were 2 instances of right ventricular preponderance, both verified by autopsy findings of right ventricular hypertrophy, 2 instances of acute right ventricular dilatation, 1 of whom had evidence of pulmonary hypertension at the time of cardiac catheterization, and 4 instances of right bundle-branch block, 2 of which were of the incomplete variety (QRS < 0.12 second).

Normal Electrocardiograms. This group included 32 patients in whom the routine electrocardiogram was essentially normal, save for 1 instance of first degree heart block and 1 with an ectopic atrial pacemaker. The only 3 instances of a nonvertical heart in the entire study were in this category. A preponderance of moderately severe emphysema existed on pulmonary function survey (25 of the 32 patients), and there were only 5 instances of moderately severe to severe emphysema detected on roentgen evaluation.

Roentgen Changes. Evaluation of the roentgenographic findings suggests that with moderately severe pulmonary emphysema as identified on function study, the chest x-ray is most likely to be interpreted as showing minimal, moderate, or moderately severe emphysema (61 of 71). Of the remaining 10 patients, 7 x-rays were interpreted as normal, with 3 instances of severe emphysema.

Of the 79 patients with pulmonary function evidence of severe pulmonary emphysema, 51 carried moderately severe to severe roentgenographic interpretations of emphysema, with another 15 instances of moderate emphysema. On consideration only of groups I, II, and III, 56 of 60 patients had moderate, moderately severe, or severe emphysema on the roentgenogram.

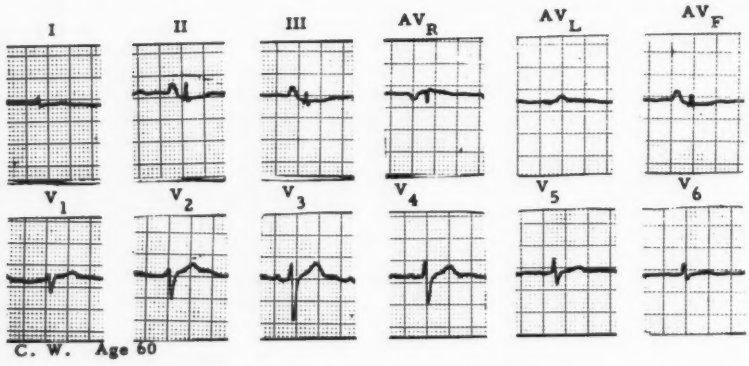
The presence of extensive parenchymal pulmonary disease, thoracoplasty defects, and lack of technically adequate lateral chest films were the major factors in the failure to identify more than minimal emphysema in the severe emphysematous group.

The patients with normal electrocardiograms and moderately severe emphysema on pulmonary function study exhibited the greatest incidence of nonexistent or minimal emphysema radiographically.

The mean cardiac rates in the 6 electrocardiographic groupings were 100, 92, 89, 100, 107, and 88, respectively.

DISCUSSION

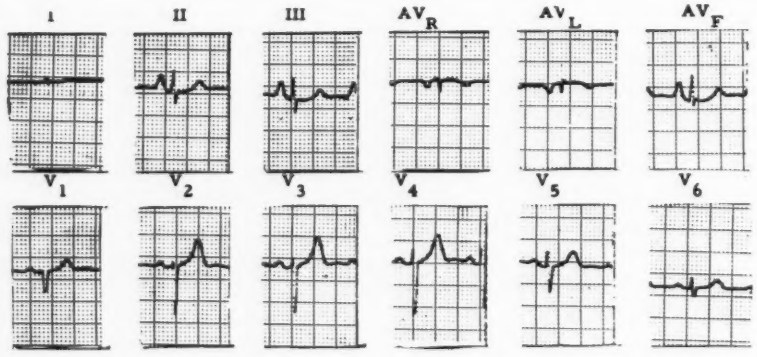
The earliest recognition of a rather distinct



C. W. Age 60

Total vital capacity = 60%
2 seconds vital capacity = 26%
Maximum breathing capacity = 22%
Single breath oxygen test: (750 - 1250 cc) = 12% N_2

X-ray: Severe pulmonary emphysema
Autopsy: Severe diffuse bullous emphysema



H. K. Age 57

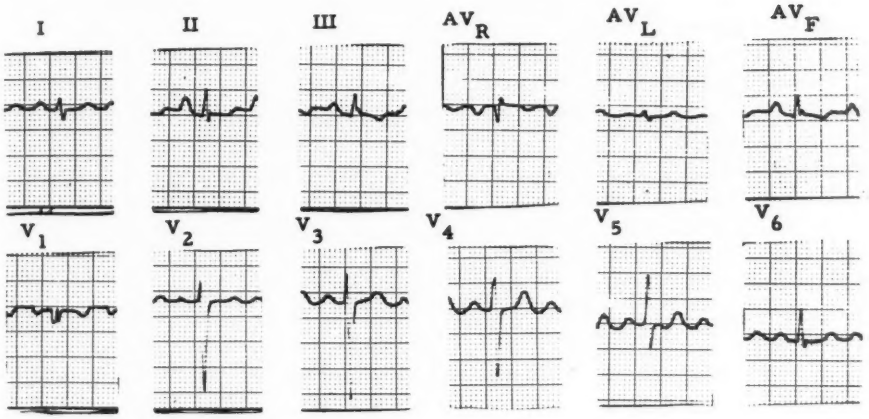
Total vital capacity = 52%
2 seconds vital capacity = 49%
Maximum breathing capacity = 44%
Single breath O_2 test: (750 - 1250 cc) = 3.5% N_2

X-ray: Severe pulmonary emphysema.

FIG. 1. Typical electrocardiographic pentalogy of pulmonary emphysema patterns. The tendency to generalized low voltage of the QRS complexes is readily appreciated.

electrocardiographic pattern in chronic cor pulmonale is credited to Zuchermann et al.,[3] who thought that this clinical state could frequently be entertained by electrocardiographic survey before it could by routine clinical methods. Their data were concerned with 50 patients with chronic cor pulmonale in whom the diagnosis was established by clinical and roentgen examinations.

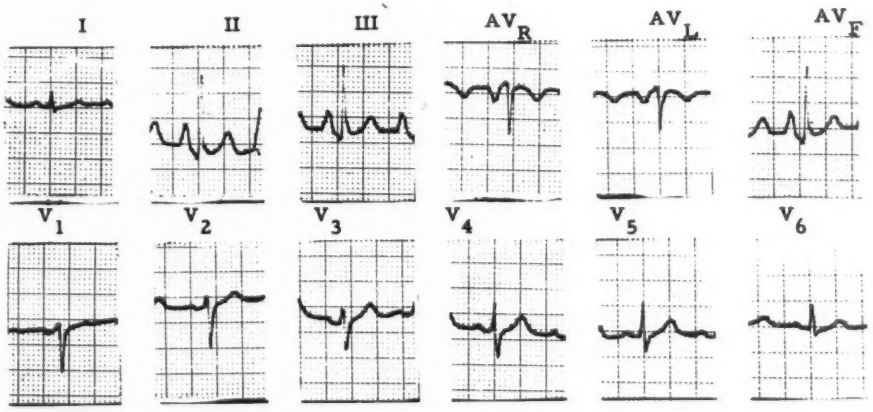
The current data were intentionally based solely on pulmonary function testing, with less than 10 per cent of the total cases presenting clinically evident chronic cor pulmonale, albeit, severe pulmonary function



C. B. Age 46

Total vital capacity = 47%
2 seconds vital capacity = 55%
Maximum breathing capacity = 43% (E)
Single breath O_2 test: (750 - 1200 cc) = 10% N_2

X-ray: Severe pulmonary emphysema



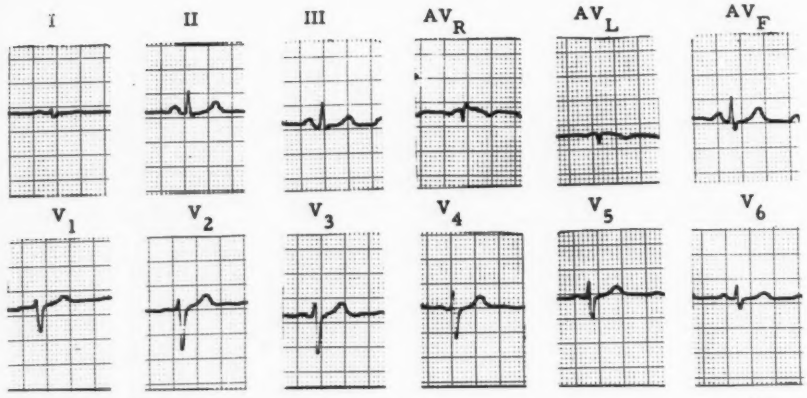
W. W. Age 61

Total vital capacity = 68%
2 seconds vital capacity = 44%
Maximum breathing capacity = 30% (E)
Single breath O_2 test: (750 - 1250 cc) = 3.5% N_2

X-ray: Severe pulmonary emphysema

FIG. 2. The degree of clockwise rotation across the precordium and the lowering of the left ventricular QRS voltage is of lesser degree than that in group 1.

leterioration. By inclusion only of patients n the severe emphysematous group, with a 2-second vital capactiy of less than 45 per cent, a maximum breathing capacity of less than 45 per cent, performed at the hyperinflation level, and a rise of the single-breath

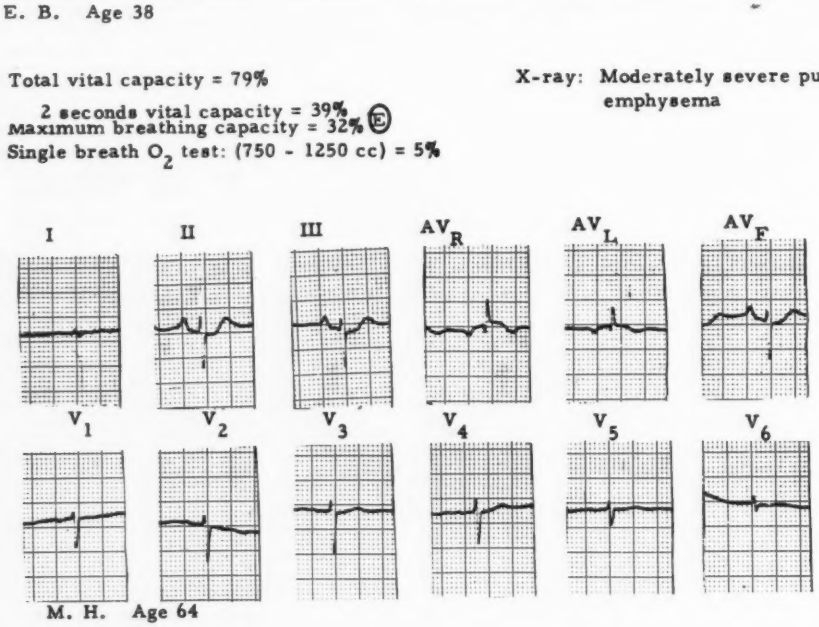


E. B. Age 38

Total vital capacity = 79%

2 seconds vital capacity = 39%
Maximum breathing capacity = 32% (E)
Single breath O_2 test: (750 - 1250 cc) = 5%

X-ray: Moderately severe pulmonary emphysema



M. H. Age 64

Total vital capacity = 65%

2 seconds vital capacity = 46%
Maximum breathing capacity = 24% (E)
Single breath O_2 test: (750 -1250 cc) = 11% N_2

X-ray: Severe pulmonary emphysema

FIG. 3 *Top.* Save for the lack of P wave and T-a-wave augmentation, the over-all pattern in group III simulates that of group I. T-a-wave inscription was either nonexistent or measured less than 1 mm. in this group.

FIG. 4 *Bottom.* Although often interpreted as showing left axis deviation and horizontal cardiac position, this pattern results from extreme vertical position of the heart, with posterosuperior reflection of the left ventricular potential to the augmented limb leads, aV_R and aV_L. Note the extremely low QRS potential in lead I and the entirely similar potentials in aV_R and aV_L, with inverted P and T waves.

xygen test of more than 8 per cent nitrogen, most select group of patients was made vailable.

As shown in table 2, the electrocardiographic pentalogy of pulmonary emphysema resents multifaceted evidence of an adanced emphysematous state, namely, predominantly severe emphysema on both pulonary function testing and roentgenographic interpretation. Thus, the finding of his electrocardiographic pattern in a known mphysematous subject suggests a severe deree of pulmonary emphysema. Seven of he 9 patients with apparent left axis deviaion were in this pentalogy grouping. It is uggested that they are, in fact, examples f extreme vertical hearts. Although Grant[4] interpreted the potential changes as due to left axis deviation, it is merely the result of the right ventricular potential reflection (rS) to leads II, III, and aV_F and left ventricular potential in a posterosuperior fashion to aV_R and aV_L. The finding of an inverted P and T wave in aV_L and the extremely low voltage QRS complex in lead I is crucial to the identification of vertical heart position (fig. 4). Radiographically, all 9 patients exhibited marked vertical hearts.

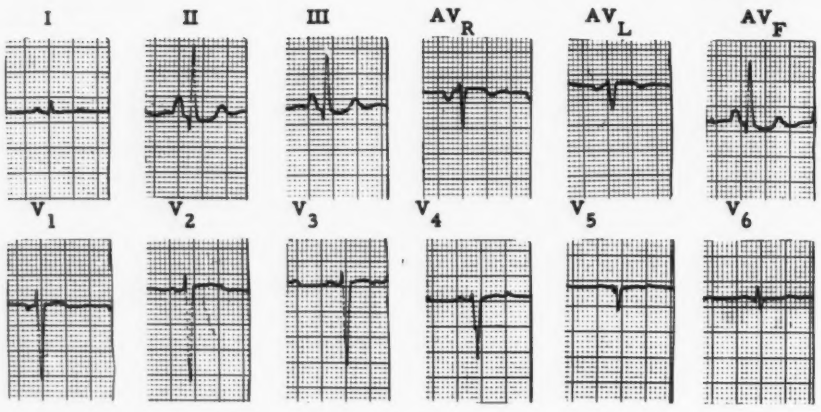
The precordial QRS complexes on occasion are grossly distorted in the pentalogy group, simulating residual myocardial damage, as previously noted by Kossmann.[5] Initial q waves may be identified in the right and mid precordial leads, or there may be failure to inscribe progressive left ventricular potentials across the precordium due to marked shift of the transitional zone to the left (fig. 5). Merely by placement of the unipolar chest lead several interspaces lower than the conventional position, normal left ventricular potential is identified (fig. 6). In some instances, left ventricular potential is best identified at the subprime positions of V_7, V_8, and V_9.

In general, the factors of vertical cardiac position, clockwise rotation, and left ventricular low voltage are considered expressions of marked vertical position of the heart attendant to the advanced emphysematous state and resultant low diaphragmatic position. The production of exaggerated P waves and resultant T-a-wave inscription is less easily explained by purely positional changes, as the classic electrocardiographic pentalogy pattern is not identified in instances of extreme vertical hearts associated with an asthenic habitus. One can only suggest the presence of incipient atrial dilatation, as entirely similar T-a-wave inscription is seen in instances of organic mitral and pulmonic stenosis. Wood[6] has previously favored an organic atrial change for the production of the T-a wave.

The partial pentalogy patterns suggest that, in general, the emphysematous state will be less severe as a group on pulmonary function testing and on roentgenographic survey.

Inasmuch as the exact mechanism for exaggerated T-a waves in pulmonary emphysema remains unknown, no explanation can be tendered for the failure to identify this phenomenon of atrial repolarization in group III. The remaining findings of vertical cardiac position, clockwise rotation, and low voltage in the standard and augmented limb leads and the left ventricular unipolar chest leads are entirely similar to those seen in group I. The short PR interval-depressed RST segment pattern often causes confusion in electrocardiographic interpretation, as the degree of RST-segment depression may be extreme, simulating changes ascribed to coronary artery disease. Failure to appreciate these changes as an expression of T-a-wave inscription secondary to pulmonary emphysema may completely alter the therapeutic approach.

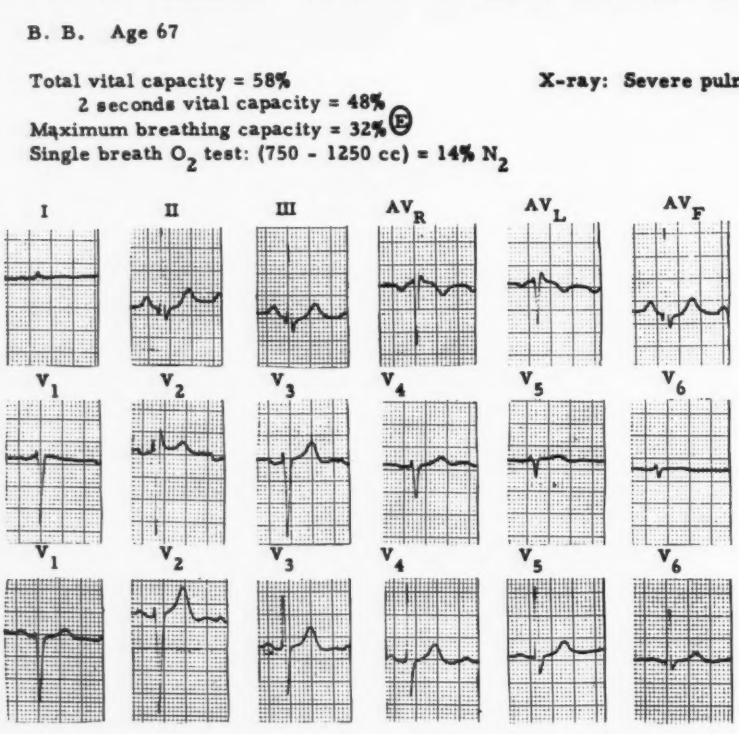
Contrary to the report of Armen, Kantor, and Weiser,[7] who reported a 27-per cent incidence of right ventricular hypertrophy on electrocardiographic survey of 67 patients with "pulmonary heart disease," an incidence of less than 2 per cent was identified in the current study. This variance may, in part, be due to an increased incidence of patients



B. B. Age 67

Total vital capacity = 58%
2 seconds vital capacity = 48%
Maximum breathing capacity = 32% (E)
Single breath O_2 test: (750 - 1250 cc) = 14% N_2

X-ray: Severe pulmonary emphysema



H. S. Age 61

Timed vital capacity = 60%
2 seconds vital capacity = 55%
Maximum breathing capacity = 42% (E)
Single breath O_2 test: (750 - 1250 cc) = 11% N_2

X-ray: Severe pulmonary emphysema.

FIG. 5 *Top.* Failure to inscribe the normal progressive increase in R-wave amplitude across the precordial leads is a common situation in the severely emphysematous patient. The distortion of the mid and left precordial QRS complexes, often simulating residual myocardial infarction, is merely the result of marked shift of the transitional zone to the left plus low

(Continued on bottom of next page)

with right heart failure in their group and to different criteria for the electrocardiographic identification of right ventricular hypertrophy. Although it is not within the scope of this paper to discuss the electrocardiographic criteria for right ventricular preponderance,* the mere findings of marked right axis deviation, various rS′r or rR′ right precordial QRS patterns, and severe degrees of clockwise rotation are insufficient criteria, as these may all result from the vertical position of the heart attendant to advanced emphysematous disease. The electrocardiographic findings in 9 patients with severe chronic cor pulmonale were previously studied[8] and the presence of a markedly elevated pulmonary artery pressure was documented where there was electrocardiographic evidence of right ventricular preponderance. Thus, it appears that the pattern of right ventricular preponderance occurs in the terminal phase of chronic pulmonary heart disease when there is hemodynamic evidence of cardiopulmonary failure. Mounsey et al.,[9] Thomas,[10] and Kilpatrick[11] have previously commented on the failure to document right ventricular hypertrophy on electrocardiographic analysis or autopsy data in advanced emphysematous disease.

Interestingly, only 2 instances of complete right bundle-branch block were identified in the entire series of 150 patients.

In the discussion of the final group, the normal electrocardiograms, it appears that from the pulmonary function and radiographic standpoints, if a normal electrocardiogram is seen in a known emphysematous patient, the degree of emphysema is apt to be of minimal to moderate severity, although individual exceptions do exist.

In general, the detection and classification of emphysema on roentgenographic interpretation correlated well with the pulmonary function data. Although there were predominant moderately severe, moderate, and minimal roentgen interpretations in the group showing moderately severe emphysema on function testing, the severe and moderately severe x-ray classifications accounted for the majority of patients with severe emphysema as detected by pulmonary function survey. Again, the presence of extensive parenchymal disease, thoracoplasty defects, and lack of lateral chest films were the major factors in failing to detect more than minimal emphysema in the severely emphysematous group. This observation is in accord with the findings of Knott and Christie,[12] who stressed the need for a lateral chest film in the roentgen interpretation of pulmonary emphysema. It is noteworthy that there was but a single instance of a roentgen report of no emphysema in the 81 patients described in the pentalogy and partial pentalogy patterns. Perhaps by continued focus on the radiographic evaluation of pulmonary emphysema, this method of examination may assume a more useful role in the evaluation of the emphysematous state.

Summary

The electrocardiographic analysis of 150 adults with moderately severe and severe pulmonary emphysema selected on pulmonary function survey has led to the identification of an electrocardiographic pattern that is highly suggestive of an advanced

*The term right ventricular preponderance is preferred to that of right ventricular hypertrophy, for one is merely interpreting electromotive potential changes and is inferring anatomic right ventricular hypertrophy.

voltage attendant to the advanced emphysematous state. Note the normal left ventricular QRS complex in leads II, III, and aV_F.

FIG. 6 *Bottom.* Normal left ventricular potential may be obtained in many of the patients presenting with advanced pulmonary emphysema merely by placing the precordial electrode several interspaces lower (*bottom strip*) than conventional placement (*middle strip*). [A previous electrocardiogram on this patient had been interpreted as showing residual myocardial damage probably secondary to previous infarction, because of failure to inscribe a normal QRS potential over the left precordial leads V_4 - V_6 (seen in the *middle strip*).]

emphysematous state. This pattern is entitled "the electrocardiographic pentalogy of pulmonary emphysema," consisting of (1) prominent P waves in leads II, III, and aV_F, (2) exaggerated T-a waves greater than 1 mm. in leads II, III, aV_F, (3) vertical cardiac position, which on occasion may be extreme, (4) marked clockwise rotation, and (5) tendency to generalized low voltage, particularly in the left precordial leads V_4 through V_7. In general, this pattern is thought to result from the extreme vertical position of the heart attendant to the advanced emphysematous state and low diaphragmatic placement, although the presence of incipient atrial dilatation cannot be discounted as a factor in the production of the exaggerated P and T-a waves.

Roentgenographic recognition of pulmonary emphysema correlated well with the pulmonary function data. In the presence of moderately severe pulmonary emphysema, the chest x-ray is most apt to be interpreted as showing minimal, moderate, or moderately severe emphysema. In the presence of severe pulmonary emphysema, moderately severe and severe emphysema will predominate on roentgenographic interpretation. The limitations of roentgenographic interpretation of pulmonary emphysema are discussed.

The T-a-wave inscription and the precordial QRS complex alteration may be of such an extreme degree that myocardial disease is suggested. Failure to appreciate these electrocardiographic changes as expressions of advanced emphysematous states may alter the therapeutic approach.

Acknowledgment

The authors are deeply grateful to Dr. J. K. Curtis and Dr. O. O. Meyer for their helpful advice and criticisms in the preparation of this manuscript, to Mrs. Lila Mulloy and Mrs. Donna Klevgaard for secretarial assistance, and to Forrest Fischer, Department of Medical Illustration, Veterans Administration Hospital, Madison, Wis.

Summario in Interlingua

Le analyse electrocardiographic de 150 adultos con emphysema pulmonar de grado moderatemente sever o sever, seligite supe le base de examines pulmono-functional, re sultava in le identification de un configura tion electrocardiographic que suggere forte mente le presentia de un avantiate stato en physematose. Iste configuration es designat como le "pentalogia electrocardiographic d emphysema pulmonar" e consiste de (1 prominente undas P in de derivationes I III, e aV_F, (2) exaggerate undas T-a, i excesso de 1 mm in le derivationes II, III, aV_F, (3) un position cardiac vertical, a vice de grado extreme, (4) marcate rotation dex trorse, e (5) le tendentia de un voltag generalistamente basse, specialmente in l derivationes precordial V_{4a7}. In general, iste configuration pare esser le effecto de position extrememente vertical del corde le qual es associate con le avantiate stato emphysematose e le basse placiamento del diaphragma, ben que le presentia de un incipiente dilatation atrial non pote esser negligite como factor in le production del exaggerate undas P e T-a.

Le recognition roentgenographic de emphysema pulmonar monstrava un bon grado de correlation con le datos pulmono-functional. In le presentia de grados moderatemente sever de emphysema pulmonar, le interpretation del roentgenogramma thoracic arriva typicamente al verdicto que le emphysema presente es de grados minimal, moderate, o moderatemente sever. In le presentia de grados sever de emphysema pulmonar, le interpretation roentgenographic nota emphysema de grados moderatemente sever e sever. Es discutite le limitationes del interpretation roentgenographic de emphysema pulmonar.

Le inscription del unda T-a e le alteration del complexo QRS precordial pote attinger grados si extreme que morbo myocardial e suspicite. Quando iste alterationes electrocardiographic non es recognoscite como expressiones de avantiate statos emphysematose le resultato pote esser le election de un non appropriate programma therapeutic.

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Medical Eponyms

By ROBERT W. BUCK, M.D.

Biot's Breathing. Camille Biot, while interne at Lyon, made a "Contribution to the Study of the Cheyne-Stokes Respiratory Phenomenon" (*Contribution à l'étude du phénomène respiratoire de Cheyne-Stokes*) which appeared in the *Lyon Médical* 23: 517-528 (December 10), 561-567 (December 17), 1876. In postscript he says:

"It would seem . . . that in meningitis the respiration is not truly Cheyne-Stokes in type, but a somewhat similar form which is more or less regular."

His observations were continued and published in a volume entitled *Clinical Experimental Studies of Cheyne-Stokes Respiration (Etude clinique et expérimentale sur la respiration de Cheyne-Stokes)*, Paris, 1878. In this volume he concludes (page 19):

"The meningitic or encephalitis type of breathing . . . is characterized by an aperiodic irregularity, by irregular pauses and sighs, without any phases of gradual increase or diminution in the respiratory movements before and after the pauses."

Transposition of the Great Vessels with Atrial Septal Defect

A Hemodynamic Study in Two Cases

By SUSAN C. LENKEI, M.D., H. J. C. SWAN, M.B., PH.D., M.R.C.P., AND JAMES W. DUSHANE, M.D.

In complete transposition of the great vessels, survival is possible only when a route of access exists by means of which venous blood may enter the lungs. This report concerns 2 patients in relatively good health in whom a high degree of mixing of venous and arterial blood occurred through an atrial septal defect. The diagnosis was established in both patients by cardiac catheterization.

ACCORDING to Keith and associates,[1] complete transposition of the great vessels is found in approximately 12 per cent of patients who die in infancy with congenital heart disease. In the classic form of this condition, the aorta arises from the right ventricle and lies anteriorly and on a plane slightly to the right of the pulmonary artery. Depending on the degree of counterclockwise rotation from 90 to 180 degrees, the position of the aorta in relation to the pulmonary artery may be variable and thus many anatomic subvariations have been described. In the basic malformation there is no arrangement by which venous blood can pass through the lungs and then to the systemic circulation; therefore this condition is incompatible with life. Valve-competent foramen ovale or atrial septal defect, ventricular septal defect, or patent ductus arteriosus, alone or in combination are the commoner pathways that allow mixing of the blood between pulmonary and systemic circulations. In approximately 40 per cent of cases the interventricular septum is closed and in approximately 8 per cent an atrial septal defect is the only communication between the two sides of the heart. Anomalous pulmonary venous drainage is rarely an associated anomaly.

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Transposition occurs more frequently in males than in females in a rato of 3:1. Evidence of the clinical triad of central cyanosis, congestive heart failure and pulmonary plethora on a roentgenogram of the thorax should cause the clinician to suspect this diagnosis. Eighty-five per cent of the patients are cyanotic at birth, and congestive heart failure develops by the age of 6 months. A third of the patients do not have an audible murmur and the intensity of the systolic murmur, when present, is variable.[2] The size of the heart is normal at birth and cardiac enlargement and the characteristic egg-shaped cardiac silhouette develop in the subsequent months. A narrow vascular pedicle in the anteroposterior position and a widened vascular pedicle in the left anterior oblique view with pulmonary plethora are often seen. The electrocardiogram is not characteristic but shows varying degrees of right-axis deviation and right ventricular hypertrophy.

The diagnosis of the transposition and any associated abnormality has been made by the use of selective angiocardiography.[3, 4] The aortic valve may lie at the level of the fourth to fifth thoracic vertebra instead of at the level of the seventh vertebra, but this relation is variable. The aorta is seen to arise anteriorly from the right ventricle.

It is the purpose of this paper to report 2 cases of complete transposition of the great vessels with atrial septal defect as the only communication between the 2 circulations. A

ositive diagnosis was established during cath-terization of the right side of the heart which ıcluded the use of indicator-dilution technics ut did not include the use of angiocardiog-aphy.

Case Reports

Case 1. The tenth child of a family was born t term after an uneventful pregnancy. He was ıtensely cyanotic at birth and spent the first week f his life in an incubator. A heart murmur was oted at the age of 3 months and the patient was eferred to the Mayo Clinic for evaluation.

On examination he was found to be well devel-ped for his age; he was moderately cyanotic vithout clubbing of the fingers or toes. A mod-rately loud systolic murmur was heard along the eft sternal border, maximal in the third and ourth intercostal spaces. The second heart sound ıt the base was loud and was not duplicated. Both emoral arterial pulses were palpable; the blood pressure was normal, and the results of the re-mainder of the physical examination were within ıormal limits. The electrocardiogram was charac-terized by sinus rhythm, right-axis deviation, and evidence of right atrial enlargement and right ven-tricular hypertrophy. The hemogram and results of urinalysis were normal. A roentgenogram of the thorax revealed the size of the heart to be with-in normal limits; the pulmonary vascular markings were normal.

The patient was seen again at the age of 2½ years. He was well developed (weight, 33 pounds; length 37½ inches); he was moderately cyanotic with clubbing of the fingers; no squatting had been noted. The results of physical examination were essentially unchanged but the thoracic roent-genogram showed some evidence of cardiac en-largement (fig. 1*a*) and polycythemia had devel-oped (hemoglobin, 16.8 Gm. per 100 ml. of blood). The saturation of systemic arterial blood as deter-mined by ear oximetry was 81 per cent at rest, 69 per cent during exercise while breathing air and 91 per cent while breathing oxygen at rest. The electrocardiogram is shown in figure 1*b*.

Catheterization[5] of the right side of the heart was carried out with the patient under balanced amnesia-analgesia[6] and breathing 100 per cent oxygen. The pressures in the great veins and right atrium were within the range of normal (table 1). The pressure in the right ventricle was severely elevated and identical to that in the fem-oral artery. At a later time the catheter passed across the midline at the atrial level to enter the left ventricle (fig. 2). There was no signifi-cant pressure gradient across the interatrial sep-tum. The central great vessels were not entered.

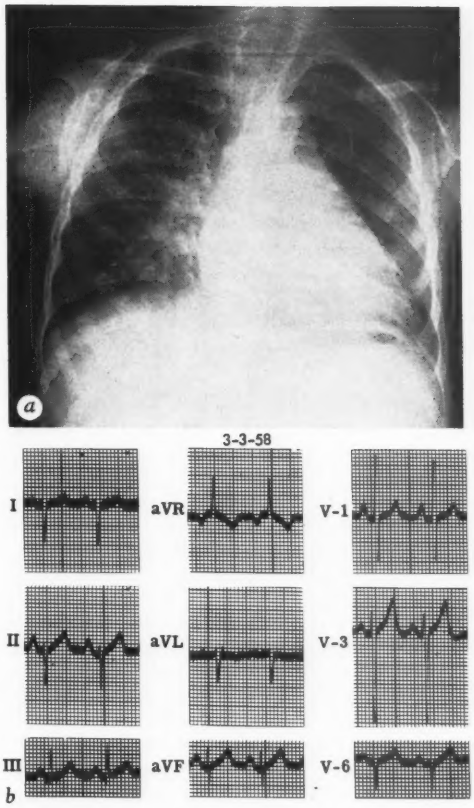

Fig. 1. Case 1. *a.* Anteroposterior view of thorax with slight rotation. Note cardiac enlargement and unusual straightening of the left cardiac border. Pulmonary vascular shadows are increased. *b.* The electrocardiogram shows right axis deviation, evidence of enlargement of the atria, and right ventricular hypertrophy.

In spite of the breathing of 100 per cent oxygen, systemic arterial blood was desaturated to 89 per cent and the saturation of mixed venous blood was reduced to 70 per cent. There was arterialization of the blood in the right atrium equivalent to a left-to-right shunt of approximately 40 per cent. The saturations of femoral arterial and right ventricular blood were not significantly different. The saturation of pulmonary venous blood was 100 per cent, and it must be presumed that a further complement was present in dissolved form, since the patient continued to breathe 100 per cent oxygen. The oxygen saturation of left ventricular blood was significantly less than that of the pulmonary venous blood. Assuming the oxygen content of pulmonary venous blood to exceed capacity by 1.8 ml. per

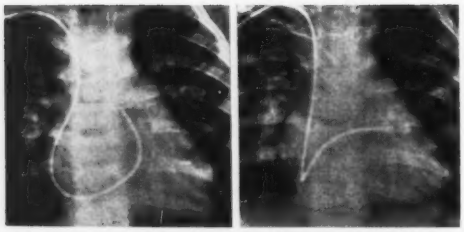

FIG. 2. Roentgenograms (case 1) showing the positions of the cardiac catheter when the tip lay in the right ventricle (*left*) and the left ventricle (*right*). It was not possible to advance the catheter to enter a great vessel from either of these positions.

100 ml. of blood, the pulmonary blood flow was calculated to be 10.7 L. per minute per M.^{2} of surface, whereas the systemic flow was 3.9 L.

An understanding of the indicator-dilution curves seen in transposition of the great vessels with intact ventricular septum may be facilitated by figure 3, which illustrates the path taken by the indicator following its injection into the right and left ventricles.

The dilution curves obtained in case 1 are shown in figure 4. The differences in appearance times and peak concentration values after injection of the dye into the 2 ventricles are apparent. All the dye injected into the right ventricle appeared to have passed directly to the systemic arterial system. In contrast, a longer appearance time, reduced peak deflection, and prolongation of the disappearance slope characterize the curve obtained after left ventricular injection. The latter are indicative of pulmonary recirculation.

The dye curves recorded after injection of indicator into the superior and inferior venae cavae are essentially similar to one another in appearance time and contour. They differ from the curve obtained after injection into the right ventricle in that the peak concentrations are smaller, and the disappearance phase fails to show the nearly complete return to zero concentration shown on the right ventricular curve. On comparison of the caval dilution curves with the latter, it appears that approximately 45 per cent of the blood draining from the superior vena cava is shunted across an interatrial communication into the pulmonary circulation and an even greater amount of blood from the inferior vena cava reaches the left atrium. This is analogous to the demonstration of a larger right-to-left shunt from the inferior than from the superior vena cava in patients without transposition who have an interatrial communication located in the fossa ovalis.[7]

The striking difference in the drainage pattern

TABLE 1.—*Pressure Measurements and Oxygen Saturations of Blood Samples in Great Vessels and Chambers of Heart in Two Cases of Transposition with Atrial Septal Defect*

Site	Case 1 Breathing oxygen Pressure (mm./Hg)	Case 1 Breathing oxygen Oxygen saturation (%)	Case 2 Breathing air Pressure (mm./Hg)	Case 2 Breathing air Oxygen saturation (%)
Superior vena cava	12/5	66	——	59
Inferior vena cava	12/8	72 to 76	——	——
Right atrium	11/7 5/–5	84 to 86	5	76 to 78
Right ventricle	97/6–12	86*	86/6–9	69
Aorta	——	——	88/67	71
Pulmonary veins	11/6	100*	10/7	——
Left atrium	14/5	——	17/7	90
Left ventricle	47/8	98	37/0–5	90
Femoral artery	96/58	89*	105/66	71
Capacity		23.7 vol. per cent		22.0 vol. per cent

*These samples were not taken simultaneously.

of blood from the pulmonary vein and the venae cavae indicates that the pulmonary veins are connected to the left atrium, while in comparison with the curve obtained after injection into the left ventricle, the shorter appearance time and greater initial deflection for the pulmonary vein curve are evidence for arteriovenous shunting at the atrial level.

Case 2. A 3-year-old boy, the first child of his family, was born at term after an uneventful pregnancy. He had been cyanotic since birth, when a heart murmur was noted. During the first 2½ years of his life this child was hospitalized many times with otitis media and repeated infections of the upper respiratory tract. At the age of 9 months he had had staphylococcal septicemia with cerebral embolism. Left residual hemiplegia and expressive aphasia developed subsequent to this illness.

On examination he was fairly well developed (weight, 31½ pounds; length, 35½ inches) with moderate cyanosis and clubbing. A moderately loud systolic murmur was heard along the left sternal border and the second sound in the pulmonic area was not duplicated. The results of neurologic examination were consistent with those associated with a right cerebral lesion.

The hemoglobin was 18.4 Gm. per 100 ml. of blood. The electrocardiogram showed the mean

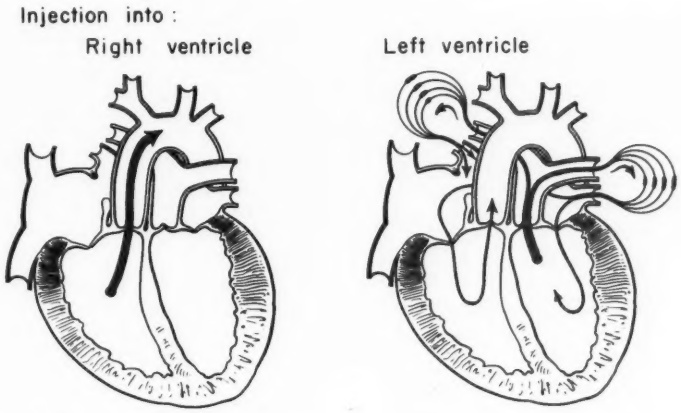

FIG. 3. Schematic representation of the heart in transposition of the great vessels with atrial septal defect showing the paths taken by dye introduced into the right ventricle (*left*) and into the left ventricle (*right*). Note the short direct circulatory path to the arterial system taken by material introduced into the right ventricle and the much longer and more complex path followed by material introduced into the left ventricle. The actual arterial dilution curves recorded in the two patients considered in this paper are shown in figures 4 and 7.

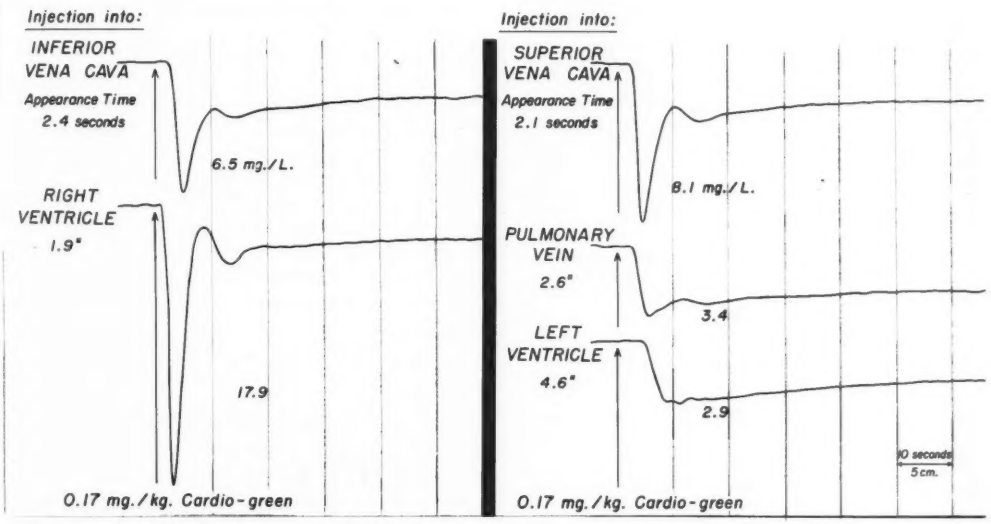

FIG. 4. Indicator-dilution curves recorded at right femoral artery in case 1. The instant of injection of dye is indicated by the vertical arrows. Note: 1. The large initial deflection followed by an almost complete clearance of dye after injection into the outflow portion of the right ventricle (fig. 2, *left*). This alone indicates that no significant flow of blood to the lungs occurs at or distal to the right ventricle. 2. The differences in magnitude of peak deflection and in contour between the curves recorded after injection into superior and inferior venae cavae and right ventricle. 3. Evidence for pulmonary recirculation in the curves recorded after injection into pulmonary vein and left ventricle. 4. Longer appearance time for curves recorded after injection into left ventricle in contrast to that for pulmonary vein, localizing the left-to-right shunt to atrial level.

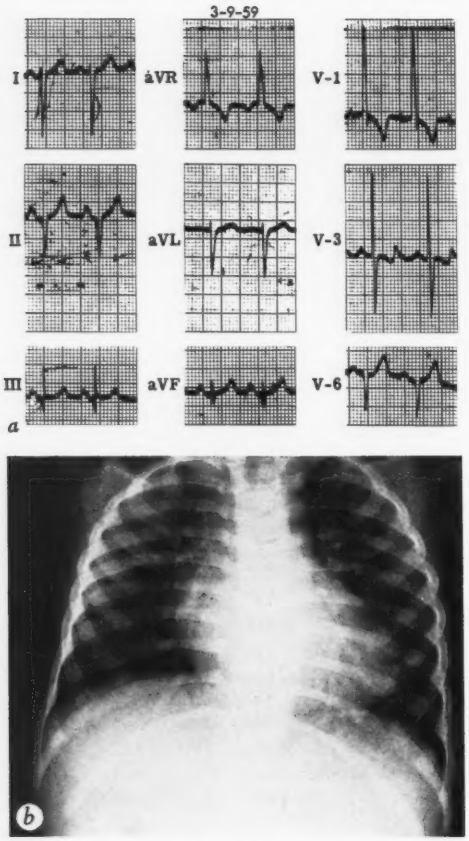

FIG. 5. Case 2. *a*. The electrocardiogram shows extreme right axis deviation with evidence of atrial enlargement and right ventricular hypertrophy. *b*. Anteroposterior view of thorax. Note slight cardiac enlargement and a moderate increase in pulmonary vascular shadows. The area usually occupied by the main pulmonary artery is concave. The aortic arch is on the left.

QRS axis to lie between 170° and 180°; there was evidence of right atrial enlargement and right ventricular hypertrophy; the left ventricular potential was not well represented by the standard electrocardiographic leads (fig. 5*a*). The roentgenogram of the thorax showed evidence of generalized cardiac enlargement with increased pulmonary vascular markings (fig. 5*b*).

The pressure in the right atrium was normal on catheterization of the right side of the heart (table 1). The right ventricular pressure was elevated and identical with that in the aorta, which was entered from the right ventricular outflow tra (fig. 6*a* and *b*). During the procedure the cath ter entered the left atrium through an atrial sept defect and was advanced into the left ventric (fig. 6*c*) where the pressure was low. There w an apparently significant pressure gradient b tween the 2 atria. The pulmonary artery was n entered.

The oxygen saturation of femoral arterial bloo of 68 per cent indicated severe systemic desatur tion and was identical with that of the right ve tricle and aorta. The saturation of mixed veno blood was likewise reduced. There was good ev dence of arterialization of venous blood at t atrial level, equivalent to a left-to-right shunt 28 per cent. Assuming a pulmonary venous oxyg saturation of 98 per cent, the drop in oxygen sa uration of blood in the left atrium must ha been due to a right-to-left shunt across the atri defect. The pulmonary blood flow, as calculate by Fick's principle, measured 8.3 L. per minu per M.^{2} and the systemic flow measured 5.2 L. p minute per M.^{2}

The dye-dilution curves are shown in figure 7. There is an obvious difference in the appearanc time, peak deflection and disappearance slope o the 2 curves after injection of dye into the right and left ventricles respectively.

Dye injected into the right ventricle appeared at the femoral artery almost immediately. The resultant dilution curve had a rapid upstroke and sharp downstroke with almost complete return to the base line, followed in 10 seconds by a second deflection. This was almost certainly due to the passage into the arterial system of indicator which had returned to the heart from the systemic circulation. Dye injected into the left ventricle passed through the pulmonary circulation before reaching the sampling site. This curve is characterized by a longer appearance time, reduced peak concentration, and a marked prolongation of the disappearance slope.

The curves obtained after dye was injected into the aorta and right ventricle, respectively, were identical and excluded any hemodynamically significant communication to the pulmonary vascular bed at or distal to the ventricular level.

Injection of dye into the superior vena cava resulted in a curve that differed from those obtained after injection into the right ventricle and aorta in that the area subtending this curve was reduced by approximately 25 per cent and the clearance of dye on first circulation was less complete. The reduction in the area of the initial portion of the curve is due to the loss of dye that had been shunted across the atrial septal defect into the left atrium while the incomplete clearance is explained

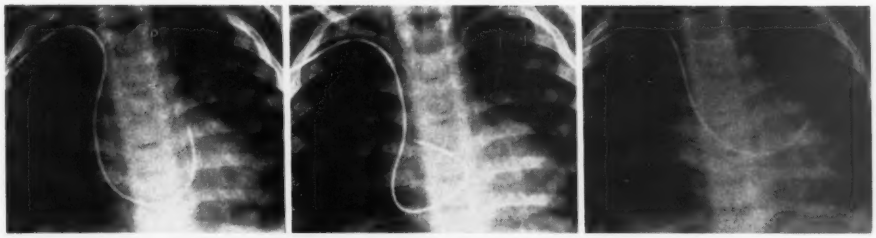

FIG. 6. Roentgenograms of the thorax showing the position of catheters in the outflow portion of right ventricle (*left*), the root of the aorta (*middle*) (proved by indicator-dilution curves) and the left ventricle (*right*). The aortic valve was not displaced cephalad and to the right as usually seen in cases of transposition. Unfortunately a lateral roentgenogram was not obtained. In each instance systolic and diastolic pressures and oxygen saturation values are given.

by the circulation of the shunted dye through the lungs. A part then re-enters the right side of the heart (shunted left to right) across the atrial septal defect. The curve recorded after injection of dye into the left atrium showed a shorter appearance time compared to that obtained after injection into the left ventricle, which served to localize the shunt to the atrial level.

DISCUSSION

In both cases the following facts were established during catheterization of the heart:

1. There are 2 anatomically and functionally separate ventricles. The systemic ventricle, which is a high-pressure chamber and supplies the high-resistance systemic arterial bed, is the anatomic right ventricle. The anatomic left ventricle is a low-pressure ventricle that supplies only the low-resistance pulmonary vascular bed. The pressure measurements alone prove the presence of separate pathways of egress from each ventricle.

2. The oxygen saturation of the femoral arterial blood is identical with that from the right ventricle and aorta and is much less than that of blood from the left ventricle. Arterialization of the caval blood takes place at atrial level, and this mixture supplies the systemic arterial system.

3. There is no further drop in the oxygen saturation of blood from the left ventricle as compared to that of the left atrium. This alone, in the presence of the significant pressure gradient across the ventricular septum,

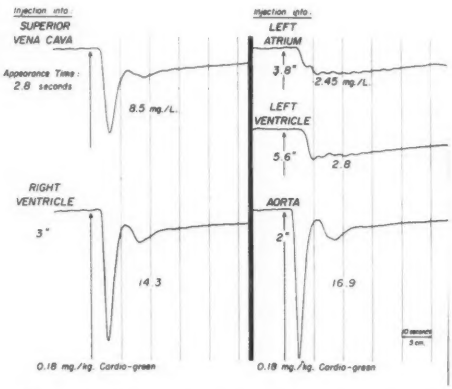

FIG. 7. Dilution curves recorded at the femoral artery in case 2. The similarity of these curves to those obtained in case 1 is apparent. Note that the second deflection for the dilution curves recorded after injection into the right ventricle and aorta is due to dye that has returned to the heart from the systemic circuit and has not passed through the lungs.

excludes any significant shunt at ventricular level.

4. The dye-dilution curves confirm the presence of 2 separate drainage pathways from the ventricles. The longer appearance time and prolonged disappearance phase found after injection into the left ventricle show that blood from this chamber first passes through the pulmonary vascular bed before a part reaches the systemic circulation. Similarly, the contour and appearance time of the dye curves after injection into the right ventricle and the aorta prove that they alone

supply the systemic circulation. At the same time the practically complete clearance of dye shown by these curves excludes any communication of significant size between the pulmonary and systemic circulations at, or distal to, the right ventricle.

The preferential shunting of blood from the inferior vena cava and the decreased peak concentration of the curves after injection of dye into the venae cavae strongly suggest the presence of an atrial septal defect located in the fossa ovalis. The short appearance time that follows injection of dye into the left atrium as compared with the longer appearance time after injection into the left ventricle localizes, in addition, a left-to-right shunt at atrial level.

5. The low pressure in the left ventricle excludes severe pulmonary stenosis or significant pulmonary hypertension.

6. The pulmonary blood flow significantly exceeds the systemic flow in both cases. The absolute magnitude of the volume shunted in both directions across the atrial septum is considerable and is related to the degree of intermixing between the right and left atrial chambers.

These findings establish the diagnosis of transposition of the great vessels with intact ventricular septum and atrial septal defect. The pressure measurements, oxygen saturation data, and dye-dilution curves cannot be explained on the basis of any other anatomic or hemodynamic abnormality.

Two additional points are worthy of comment. From the clinical point of view it is remarkable that at no time did either patient have any symptom or sign of congestive heart failure considered characteristic of this condition. This is almost certainly related to the substantial degree of mixing that was apparently occurring freely at atrial level.

In figure 6*b* the roentgenogram made with the tip of the cardiac catheter lying just above the aortic valve suggests that the location of this valve may be normal and not at the level of the fourth thoracic vertebra as has been described in complete transposition of the great vessels.[1] This may represent transposition type I of Castellanos and associates.[3]

Summary

The cardiac catheterization findings in 2 patients, aged 2½ and 3 years, with moderate physical disability due to cyanotic congenital heart disease are reported. In each patient, 2 ventricles were entered, the left with a low level of pressure and a high blood-oxygen saturation, the right with pressure equal to systemic arterial pressure and a reduced blood-oxygen saturation equal to that of systemic arterial blood. It was demonstrated by indicator-dilution curves that all blood from the right ventricle passed into the systemic circulation, while all blood from the left ventricle passed into the pulmonary circulation. Mixing of systemic venous and pulmonary venous bloods at atrial level was also demonstrated. On these hemodynamic data the diagnosis of complete transposition of the great vessels with atrial septal defect was made.

Summario in Interlingua

Es reportate le resultatos de catheterismo cardiac in 2 patientes, de 2½ e 3 annos de etate, con moderate grados de invaliditate physic como effecto de congenite morbo cyanotic del corde. In ambe casos, penetration de ambe ventriculos esseva effectuate, le ventriculo sinistre con un basse nivello de pression e un alte saturation de oxygeno, le ventriculo dextere con un pression equal al pression arterial in le circulation major e un saturation oxygenic del sanguine reducite al nivello trovate in le sanguine arterial del circulation major. Esseva demonstrate per curvas de dilution de un indicator que omne le sanguine ab le ventriculo dextere passava a in le circulation major durante que omne le sanguine ab le ventriculo sinistre passava a in le circulation pulmonar. Esseva etiam demonstrate le mixture de sanguines venose del duo circulationes al nivello atrial. Super le base de iste datos hemodynamic le diagnose de un transposition complete del grande vasos in association con defecto atrio-septal esseva formulate.

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Truly America has a great future before her; great in toil, in care, and in responsibility; great in true glory if she be guided in wisdom and righteousness; great in shame if she fail. I cannot understand why other nations should envy you, or be blind to the fact that it is for the highest interest of mankind that you should succeed; but the one condition of success, your sole safeguard, is the moral worth and intellectual clearness of the individual citizen. Education cannot give these, but it may cherish them and bring them to the front in whatever station of society they are to be found; and the universities ought to be, and may be, the fortresses of the higher life of the nation.—THOMAS H. HUXLEY. *American Addresses with a Lecture on the Study of Biology.* London, MacMillan and Co., 1877, p. 126.

Pulmonary Resistance in Acquired Heart Disease

By Bernard L. Charms, M.D., Bernard L. Brofman, M.D., and Paul M. Kohn, M.D.

Disproportionately high pulmonary artery pressures and pulmonary vascular resistance in acquired heart disease, particularly mitral stenosis, have been repeatedly observed. Seventeen patients with pulmonary hypertension secondary to elevated left atrial pressure have been studied by the method of temporary unilateral pulmonary artery occlusion: Resistances calculated before and after occlusion showed no change in most cases. The data show that despite very high initial resistance, increase in flow in the lung can occur with rapid reduction in resistance. It is suggested that "tone" of the pulmonary vasculature is operative even at very high pressure levels.

PULMONARY vascular changes associated with pulmonary hypertension have been demonstrated in congenital heart disease causing increased pulmonary blood flow[1-3] and similar pathologic changes in the pulmonary arterioles occur in patients with mitral stenosis.[4] The factors leading to the medial hypertrophy and intimal proliferation are not known; the role of vascular tone has been difficult to assess. It is well known, however, that the degree of pulmonary hypertension, especially in cases of mitral stenosis, may be disproportionately great relative to the left atrial pressure, and the calculated pulmonary resistances may be exceedingly high.[5-7] The excessive resistance to flow in the lungs is considered to be due either to the pathologic changes in the pulmonary arteries and arterioles or to an increase in tone of pulmonary arterioles, thus protecting the lung from edema. Increase in blood flow with exercise causes an increase in pulmonary artery pressure[8] that can be due to resistance in the pulmonary vascular bed or in the left atrium or left ventricle. The studies herein presented suggest the presence of "tone" in the pulmonary vascular tree, despite high resistance at rest.

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The pulmonary pressure-flow relationship have been studied by the method of temporary unilateral pulmonary artery occlusion in patients with acquired heart disease. Previous reports[8, 10-14] have shown no obligate relationship between pressure and flow in normal subjects or in patients with pulmonary disease, except in the presence of granulomatous lung disease with diffuse fibrosis involving the pulmonary vessels,[11] when an increase in flow necessitates a proportionate increase in pressure. Temporary unilateral pulmonary artery occlusion is a unique method for increasing flow through a portion of the pulmonary bed without any pharmacologic effects or the physiologic effects of exercise.

Methods and Materials

The patients studied are listed in table 1 with the diagnoses. There are 5 with "pure" mitral stenosis, 3 with mitral stenosis and associated insufficiency or aortic stenosis, 4 with "pure" mitral insufficiency, 3 with congestive failure secondary to rheumatic or coronary artery heart disease, and 1 with severe congestive failure due to myocardial sarcoidosis proved at postmortem examination.

Cardiac catheterization was carried out in the usual manner in a resting postabsorptive state under light sedation, usually secobarbital 0.1 Gm. A previously described[10] special triple-lumen cardiac catheter with an inflatable cuff on the middle lumen was inserted via an antecubital vein and advanced under fluoroscopic guidance into either right or left main pulmonary artery. An indwelling arterial needle was placed in the brachial or

moral artery. Control values were obtained after suitable period of time. Although the patients ere not in a basal state, we believe a relative teady state" was achieved, since oxygen conmption, cardiac outputs, and pressures were able throughout. Blood samples were aspirated om the pulmonary artery and brachial or femral artery and analyzed for oxygen content by e spectrophotometric method of Hickam and raser[15] or by the manometric technic of Van lyke and Neill.[16] Oxygen consumption was dermined in some cases on a Collins spirometer nd, in most, by collection of expired air and analsis on a Pauling Beckman model C oxygen anayzer. Pressures were recorded by a Sanborn lectromanometer and a Statham strain gage with multi-channel direct writer. Cardiac outputs ere calculated according to the Fick principle nd pulmonary resistances by the standard formuas for pulmonary arteriolar resistance,[14]

$$R = \frac{PA\ (mean) - LA\ (mean) \times 1{,}333.4\ dynes \times 60\ second}{CO\ (L./min.) \times 1{,}000\ cm.^5}$$

After determination of control values, the cuff was inflated in either right or left main pulmonary artery; complete occlusion was ascertained by observing a fall in pressure in the pulmonary artery distal to the cuff to "pulmonary capillary" levels and obtaining fully oxygenated blood from the pulmonary artery distal to occlusion. Usually a slight increment in pulmonary artery pressure occurred, which remained until deflation. After 10 to 20 minutes, repeat studies were obtained. There were no untoward reactions, and the patients were asymptomatic.

Results

All patients had elevated pulmonary artery pressures ranging from 35/18, with a mean of 26 mm. Hg in case 1, to 120/70, with a mean of 90 mm. Hg in case 16 (table 2). There was close agreement between the wedge pressures obtained in the usual manner and those distal to the inflated cuff. Where wedge pressures were not obtained, the distal pressure was used for calculation of resistances, both initially and after occlusion. These pressures were elevated in all but case 9, the range being 12/8 (mean 10 mm. Hg) to 43/12 (mean 35 mm. Hg). The arteriovenous differences were elevated in those with severe congestive failure and were normal in those patients well compensated at the time of the study. Cardiac outputs, as expected, tended to be low.

Table 1.—*Clinical Data*

	Patient	Age	Sex	Surface area	Diagnosis
1	A.G.	19	F	1.46	Mitral insufficiency
2	D.E.	58	M	1.96	Coronary artery disease, congestive failure
3	R.Y.	33	F	1.68	Mitral stenosis
4	E.W.	53	M	1.57	Mitral stenosis
5	H.V.	61	M	2.20	Congestive failure, rheumatic heart disease
6	C.S.	55	M	1.78	Mitral insufficiency, rheumatic heart disease
7	C.S.	37	M	2.22	Coronary artery disease, congestive failure
8	B.S.	20	F	1.57	Mitral stenois
9	E.S.	34	F	1.47	Mitral insufficiency, rheumatic heart disease
10	J.R.	20	M	1.24	Mitral stenosis, possible congenital
11	G.P.	36	M	1.81	Mitral and aortic stenosis
12	A.P.	38	F	1.49	Mitral insufficiency, rheumatic heart disease
13	E.M.	55	F	1.65	Mitral stenosis, aortic stenosis
14	C.H.	57	M	1.77	Mitral stenosis and insufficiency
15	R.H.	43	M	1.70	Mitral stenosis
16	B.B.	22	F	1.55	Mitral stenosis
17	E.O.	25	F	1.53	Myocardial sarcoidosis, congestive failure

The most striking result was the absence of any marked pressure increment in the pulmonary artery after occlusion of the circulation to one lung in all but case 13. In this instance, the pressure did rise considerably although it was not in direct proportion to the estimated doubling of flow through the unoccluded lung. The remaining cases showed little or no change, even in those cases where the control pressures reached or exceeded 100 mm. Hg. Since over-all cardiac outputs were changed but little, it is apparent that the unoccluded lung was now carrying approximately twice the control flow. Arterial blood hemoglobin saturations, heart rate, and systemic pressures also showed no significant change. Respiratory minute

TABLE 2.—*Catheterization Data*

	Patient*	Pulmonary artery pressures (mm.Hg) S	D	M	Wedge or distal (mm.Hg)†	O Consumption (ml./min.)	A-V Difference (Volume per cent)	Cardiac output (L./min.)	Cardiac index (L./min./SM.²)	Pulmonary arteriole resistance (Dynes sec/cm.⁻⁵)
1	A.G.									
	C	35	18	26	20-8 (14)	294	4.6	6.4	4.4	150
	O	50	25	34	20-8 (14)	366	4.8	7.6	5.2	210
2	D.E.									
	C	82	30	52	38-15 (27)	471	8.9	5.3	2.7	377
	O	82	40	56	42-20 (30)	525	7.6	7.0	3.6	297
3	R.Y.									
	C	100	55	70	30-20 (25)					
	O	100	50	66	30-20 (25)					
4	E.W.									
	C	38	20	28	24-15 (20)	196	5.9	3.3	2.1	194
	O	45	18	30	22-16 (19)	250	5.6	4.5	2.9	196
5	H.V.									
	C	74	40	56	33-20 (26)	308	5.3	5.8	2.6	414
	O	75	42	57	33-20 (26)	342	6.2	5.5	2.5	450
6	C.S.									
	C	65	30	42	30-10 (20)	167	6.6	2.5	1.4	704
	O	62	26	40	25-12 (19)	175	5.8	3.0	1.7	560
7	C.S.									
	C	60	30	42	25-12 (19)	273	10.0	2.7	1.2	682
	O	62	35	45	25-12 (19)	269	7.3	3.7	1.7	562
8	B.S.									
	C	40	20	30	26-18 (20)	167	3.0	5.6	3.6	143
	O	50	20	32	26-18 (20)	192	3.2	6.0	3.8	160
9	E.S.									
	C	40	20	28	12-8 (10)	102	4.9	2.1	1.4	686
	O	42	18	30	12-8 (10)	168	5.6	3.0	2.0	533
10	J.R.									
	C	100	45	70	30-25 (27)	147	6.1	2.4	1.9	1432
	O	110	57	80	35-20 (27)	179	7.1	2.5	2.0	1692
11	G.P.									
	C	62	39	49	35-30 (32)	211	6.1	3.5	1.9	389
	O	70	43	53	35-30 (32)	242	6.0	4.0	2.2	428
12	A.P.									
	C	98	35	55	35-15 (26)	338	7.9	4.2	2.8	552
	O	95	35	55	38-15 (27)	365	8.5	4.3	2.9	522
13	E.M.									
	C	65	30	45	30-22 (27)	185	5.0	3.7	2.2	389
	O	100	40	60	35-24 (30)	185	5.5	3.4	2.1	706
14	C.H.									
	C	78	20	43	30-10 (20)	250	5.4	4.6	2.6	400
	O	80	25	45	30-10 (20)	184	5.7	3.2	1.8	625
15	R.H.									
	C	60	35	45	40-30 (34)	226	6.2	3.6	2.1	244
	O	70	35	50	30-25 (28)	225	6.1	3.6	2.1	490
16	B.B.									
	C	120	70	90	40-30 (35)	196	7.0	2.8	1.8	1570
	O	120	70	90	43-20 (32)	224	9.3	2.4	1.6	1933
17	E.O.									
	C	65	32	45	35-18 (27)	234	4.8	5.6	3.6	257
	O	65	30	48	43-12 (28)	378	5.9	6.4	4.2	250

†Figures in parenthesis are mean pressures. C, control values; S, systolic; O, occlusion of either right or left main pulmonary artery; D, diastolic; M, mean.

volumes increased only 10 to 20 per cent following occlusion, despite the fact that the occluded lung continued to ventilate and the entire oxygen consumption was occurring in the unoccluded lung.

The calculated pulmonary resistances show the most striking effects. Except for cases 3 and 15, there is little change in arteriolar resistance. If one assumes, however, that the resistance during the control studies is shared equally by the 2 lungs, it is apparent that following occlusion of one main pulmonary artery, the resistance of the unoccluded lung has become abruptly one half of its previous level, since it carried twice the flow with the same pressure gradient. This abrupt change in resistance was accomplished with marked rapidity, since any pressure change occurred immediately with inflation of the cuff and remained constant until deflation. In cases 13 and 15, however, the resistance in the pulmonary vascular bed was apparently fixed so that with increase in flow there was a proportionate rise in pressure gradient. Although an accurate cardiac output was not obtained in case 3, it is included because of the marked pulmonary hypertension present at rest and no change following occlusion.

In many of the patients exercise was carried out and pulmonary artery or wedge pressures rose markedly as has been shown by others.[8]

Discussion

The most surprising findings in this group of patients was the absence of any significant increase in pulmonary artery pressure following occlusion of one main branch of the pulmonary artery. Since total cardiac output was changed very little, it is evident that a 2-fold increase in flow in the unoccluded lung was accomplished, despite severe pulmonary hypertension, and hence a striking decrease in pulmonary arteriolar resistance had occurred. In only 2 of the 17 cases (13 and 15) was there a direct relationship between resistance and flow. In all other cases, resistance decreased in the unoccluded lung by approximately 50 per cent. Exercise would increase pulmonary artery pressure and if there were increase in cardiac output and a static left atrial pressure assumed, calculated resistance would increase. The apparent increase in pulmonary arteriolar resistance would not be genuine but simply due to further increase in left atrial pressure. The presently described method obviates changes in over-all cardiac output and gross changes in left atrial pressure and thus permits a more precise evaluation of the pulmonary vascular bed.

The patients with the most marked pulmonary hypertension and highest pulmonary resistance showed remarkable ability to decrease the resistance of the unoccluded lung. Since the pathologic changes in the pulmonary arteries and arterioles are most likely found in such patients, it is apparent that other factors must play an important role in determining the resistance. The rapidity of the decrease in resistance in the pulmonary vascular bed following occlusion of the contralateral lung is striking. The concept of a "critical closing pressure" seems most applicable here.[17, 18] The critical intravascular pressure necessary to keep these vessels open may be greatly elevated owing to thickening or spasm of the vessel walls, as well as to increased tissue pressure. Once this critical pressure is exceeded, however, large increases in flow may occur without significant increase in pressure gradient. It is quite possible that the extravascular factor of increased tissue pressure may be due to increased bronchomotor tone as is most clearly seen clinically in patients with cardiac asthma.[19] The bronchial constriction creates expiratory obstruction causing an increase in intrapleural and intrapulmonic pressure, thus tamponading the small pulmonary vessels and elevating the critical closing pressure in the capillaries.

Reflex relaxation of the pulmonary arterioles may also be considered to explain the decrease in vascular resistance.[20] A humoral mechanism seems unlikely in view of the rapidity of the change. It is difficult to explain why those patients with the highest

pulmonary artery pressures could decrease resistance so readily, while others with considerably less initial resistance, could not. The mechanism involved seems to be quite independent of the level of pulmonary artery pressure or resistance.

Summary

Seventeen patients with acquired left-sided heart disease and pulmonary hypertension were studied by means of temporary unilateral pulmonary artery occlusion. Only 1 patient evidenced significant rise in pulmonary artery pressure and only 2 showed significant increase in resistance.

Pulmonary artery occlusion increases pulmonary flow without change in cardiac output or left atrial pressure and, therefore, tests the adaptability of the pulmonary vasculature alone. Despite very high initial pulmonary resistance, increase in flow was accommodated with sudden sharp decline in resistance. The mechanism of this adaptability in the lung is discussed.

Acknowledgment

We wish to thank Drs. R. I. Newman and J. Elder for their participation in these studies and Mrs. M. Rizieka, Mrs. J. Germano, and Miss M. Alford for their technical assistance.

Summario in Interlingua

Dece-septe patientes con acquirite morbo sinistro-cardiac e hypertension pulmonar esseva studiate per medio de occlusion temporari unilateral de arteria pulmonar. Solmente 1 del patientes exhibiva un augmento significative del tension pulmono-arterial, e solmente 2 monstrava augmentos significative del resistentia.

Occlusion de arteria pulmonar augmenta le fluxo pulmonar sin alterar le rendimento cardiac o le tension sinistro-atrial e, per consequente, representa un test del adaptabilitate del vasculatura pulmonar sol. In despecto de altissime nivellos initial de resistentia pulmonar, le augmento del fluxo esseva absorbit e per un multo acute reduction del resistentia. Le mechanismo de iste adaptabilitate del pulmon es discutite.

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The physician needs a clear head and a kind heart; his work is arduous and complex, requiring the exercise of the very highest faculties of the mind, while constantly appealing to the emotions and finer feelings. WILLIAM OSLER.—*Teaching and Thinking.* Montreal Med. Journal, 1895.

Primary Arteritis of Abdominal Aorta in Children Causing Bilateral Stenosis of Renal Arteries and Hypertension

By T. J. Danaraj, M.D., M.R.C.P.E., and Wong Hee Ong, M.B.

The clinicopathologic findings are described in 2 children in whom a localized arteritis of the abdominal aorta had occluded both renal artery orifices to produce hypertension. The relation to primary arteritis of the aortic arch or Takayashu's syndrome is discussed.

RECENT reports[1-6] have emphasized the importance of recognition and satisfactory surgical treatment of patients suffering from hypertension due to unilateral renal artery stenosis caused by embolism, thrombosis, atherosclerotic plaques, or aneurysms. Most cases have been in adults and the diagnosis of the obstruction was made by aortography. The purpose of this paper is to draw attention to the occurrence of hypertension in children as a result of stenosis of the orifices of both renal arteries by a localized arteritis of the abdominal aorta. As in adults, aortography would enable the recognition of such lesions and lead to possible surgical cure.

Case Reports

Case 1. A 7-year-old Chinese girl was admitted to the General Hospital, Singapore, on March 21, 1955, because of difficulty in breathing, epigastric discomfort, swelling of the feet, and puffiness of the face. She had been in good health until 3 weeks previously when attacks of breathlessness and discomfort in the epigastrium occurred and became progressively worse. Swelling of the feet, diminished urinary output, and slight puffiness of the face occurred 1 week before admission. There were no general symptoms or history of recent sore throat or any other infection.

Physical examination revealed a very sick girl, with pale and slightly puffy face, engorged neck veins, dyspnea, and restlessness. There was no fever. The pulse rate was 112 per minute. There was slight pitting edema of the feet, and a forceful apical beat was felt in the fifth left intercostal space 10 cm. from the midsternal line. The second sound in the pulmonic area was louder than the second aortic sound. Gallop rhythm and a soft systolic murmur of moderate intensity were heard in the mitral area. The blood pressure was 125/110 mm. Hg and equal in both arms; the arterial pulses in the lower extremities were distinctly palpable. The fundi were normal.

Examination of the lungs revealed normal findings. The liver was enlarged 4 fingerbreadths below the costal margin and was tender; the spleen and kidneys were not felt.

The hemoglobin was 9.6 Gm. per 100 ml., the erythrocyte count was 3,370,000, and the leukocyte count was 13,000 per mm.^{3} with a differential count of 78 per cent polymorphonuclear cells, 20 per cent lymphocytes, and 2 per cent monocytes. The plasma proteins were 4.67 Gm. per 100 ml.; albumin 3.14, globulin 1.35, and fibrinogen 0.18 Gm. per cent. Examination of urine revealed a specific gravity of 1.010, 1+ albumin, and a few pus, red blood, and epithelial cells per high-power field; a few granular casts were also present. An x-ray film of the chest showed an enlarged heart, with congestion of the lungs.

The clinical course was characterized by a persistently elevated blood pressure (140 to 110 over 115 to 90 mm. Hg) and intractable cardiac failure. Response to treatment with digitalis was poor and complicated by numerous ventricular extrasystoles. Injections of mersalyl produced no significant diuresis. The urinary output varied between 15 and 25 ounces a day, the specific gravity of the urine being between 1.006 and 1.012; no albumin was found nor were casts seen in centrifuged deposits. Frequent estimations of the blood urea gave normal levels until 5 days before death, when it was 46 mg. per 100 ml.

Puffiness of the face disappeared, but slight edema of the feet persisted. A second radiologic examination of the chest showed a further increase of the cardiac shadow and persistent pulmonary congestion. She died 46 days after admission to the hospital.

At necropsy the heart was enlarged with hypertrophy and dilatation of the left ventricle. The endocardium was smooth, and there was a small adherent thrombus below the anterior cusp of the aortic valve; there were no valvular defects. The

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coronary arteries were smooth and of normal caliber. On the intimal surface of the aorta were 3 strictly localized plaques of thickened intima (figs. 1 and 2). The first, situated just above the posterior cusp of the aortic valve, was 1 by 0.5 cm. in diameter. The second, on the arch of the aorta just distal to the origin of the left subclavian artery, was 2 by 3 cm. and had a red thrombus superimposed on it, while the third and largest involved the entire circumference of the abdominal aorta, extending from the origin of the celiac artery to just below the level of the ostia of the renal arteries. The affected area measured 3.5 cm. in length and was covered by large adherent red thrombi that had occluded the orifice of the superior mesenteric artery. The ostia of the celiac artery and both renal arteries were considerably narrowed by the thickened intima and obscured by the thrombi. The arteries themselves were of normal caliber and showed no abnormality. The rest of the aorta was normal.

Both suprarenal glands and left kidney were normal. There was a depressed scarred area on the convex border of the posterior surface of the right kidney, which was slightly smaller than the left. The lungs were edematous and congested. The liver was enlarged and firm, and its cut surface exhibited the characteristic appearance of chronic venous congestion. The spleen was normal in size, but congested. The other organs showed no changes. The skull was not opened.

The histologic appearance of sections of the left ventricle were those of hyperplasia and hypertrophy of the myocardium. A small adherent thrombus was present on the endocardial surface below the aortic valve (fig. 3). There was no thickening of the endocardium or inflammation or fibrosis of the myocardium. Sections of the aorta (fig. 4) taken from the areas of the 3 plaques showed marked thickening of the intima with areas of ulceration and thrombus formation. The intima consisted of loose connective tissue with areas of hyalinization in the deeper layers and organization of the thrombi on the surface. The media showed fairly well marked vascularization and patchy areas of destruction with replacement by collagen. Necrosis of the media was most marked in those areas where there was ulceration of the overlying intima. Focal infiltration of the media and adventitia mostly by lymphocytes, but also by some plasma cells was a chief feature; these cells were mainly perivascular in distribution (fig. 5). The adventitia was thickened, with increased vascularization, but endarteritis was not present. These pathologic changes although involving the aorta adjacent to the ostia of the renal, superior mesenteric, and celiac arteries, had not extended into the arteries themselves. No organisms were seen. Sections of the renal arteries and of the aorta between the 3 plaques revealed no abnormality.

FIG. 1. Case 1. Hypertrophied left ventricle and aorta with the first plaque just above the aortic valve and the second on the arch just distal to the origin of the left subclavian artery. An adherent thrombus overlies the second plaque.

Except for multiple infarcts situated mainly in the cortex of the right kidney, there were no abnormalities in either kidney. The intrarenal arteries showed no hypertrophy or degenerative changes and there was no proliferation of the intima. The histologic changes found in the spleen and liver were those of chronic venous congestion.

Case 2. A Chinese boy aged 13 years was hospitalized because of increasing drowsiness and fits. He was well until 3 months prior to admission, when he developed a low-grade irregular fever and cough. On the day of admission he was found to be drowsy and had twitchings of the face and mouth, with clonic movements of all limbs.

On examination the boy was unconscious and having generalized fits; the temperature was 101 F., the pulse rate 100, and the respiratory rate 32 per minute.

The heart was enlarged to the left, with a forceful apical beat in the sixth left intercostal space in the anterior axillary line. The second sound in the aortic area was loud and ringing; there were no murmurs. The blood pressure was 160/120 mm. Hg in both arms; the femoral pulses were easily felt. The lungs were clear, and the liver, spleen, and kidneys were not palpable. The neck was rigid, and a positive Kernig sign was elicited. The limbs were flaccid, with absent tendon reflexes

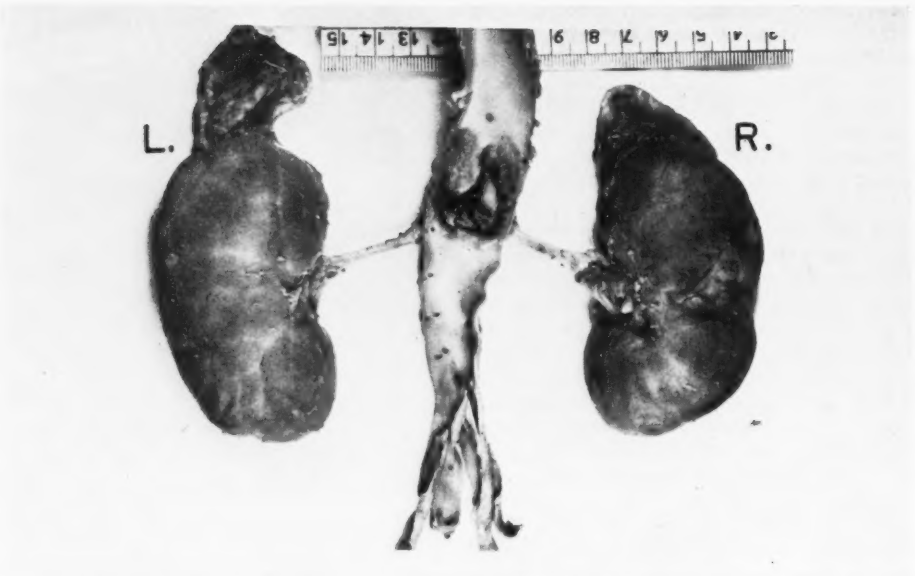

FIG. 2. Case 1. Abdominal aorta with third plaque. The overlying thrombi obscure the orifices of the renal arteries. Depressed scar on posterior surface of right kidney, which is slightly smaller than left.

and bilateral Babinski response. The pupils were dilated and nonreactive, and examination of the fundi showed no abnormality.

The hemoglobin was 10.9 Gm. per 100 ml. and the leukocyte count was 18,400 per mm.^{3} with 86 per cent polymorphonuclear cells. Examination of the blood urea was 55 mg. per 100 ml.; blood culture and a Kahn test were negative. The urine, which had a specific gravity of 1.015, contained 1+ albumin and few red blood cells and pus cells per high-power field.

The patient was treated as for hypertensive encephalopathy and also given penicillin. He became less drowsy, regained consciousness, and on the fifth day his temperature became normal.

Repeated urinalyses revealed in the centrifuged deposit about 60 to 70 red blood cells per field with occasional pus cells and granular casts; the specific gravity was normal. *Escherichia coli* were cultured from the urine once. Radiologic examination revealed an enlarged heart with a prominent left ventricle and congestion of the lungs. There was no appreciable difference in the size of the kidneys and intravenous pyelograms were normal. A Regitine test was negative. The hypertension persisted, varying between 130 to 190 mm. Hg over 120 to 150 mm. Hg. After 18 days congestive cardiac failure appeared and 4 days later the patient died.

At necropsy the heart was enlarged and the left ventricle markedly hypertrophied. The endocardium was smooth and not thickened, but below the aortic valve there was a small adherent thrombus. The valves showed no abnormality. The aortic arch and descending thoracic aorta were of normal caliber, and the intima was smooth and glistening except for a few small flecks of atheroma around the orifices of the branches of the arch. The abdominal aorta was normal except for a clearly demarcated area 8.5 cm. long extending from 1 cm. above the origin of the celiac artery to just above the origin of the inferior mesenteric artery (fig. 6). This segment of the aorta was uniformly dilated and its intimal surface presented a swollen appearance with irregular raised plaques, some of which had ulcerated, with formation of adherent thrombi. The origin of both renal arteries was involved in this pathologic process resulting in considerable narrowing of the left ostium and occlusion of the right (fig. 7). The right renal artery, which was larger than the left and felt like a cord, contained a thrombus extending from the aortic orifice of the artery along its entire course up to its bifurcation at the hilum of the kidney. The ostium of the left renal artery presented a small slit-like appearance due to swelling and puckering of the adjacent intima; the lumen of the artery along its entire length contained a slender

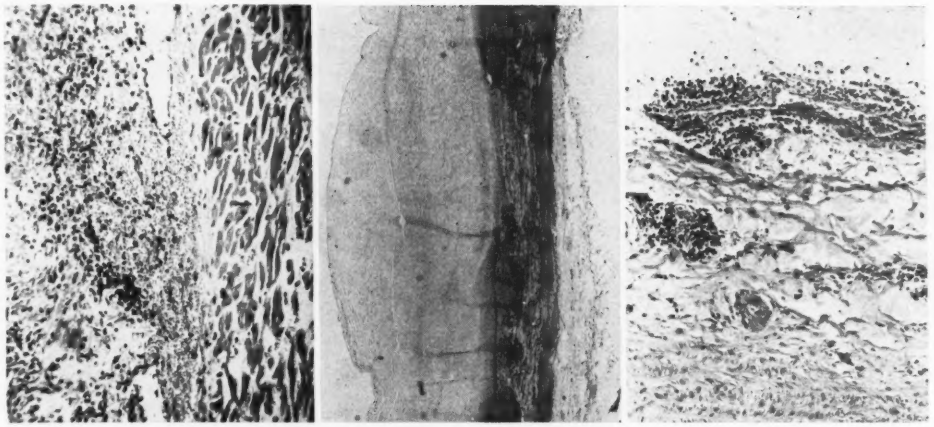

FIG. 3 *Left*. Case 1. Section of myocardium showing adherent thrombus on endocardial surface. Hematoxylin and eosin stain. × 135.

FIG. 4 *Middle*. Case 1. Marked thickening of intima and patchy areas of destruction in media at the level of the plaque in the abdominal aorta. Verhoeff-van Gieson stain. × 40.

FIG. 5 *Right*. Case 1. Infiltration of adventitia by lymphocytes and plasma cells, mainly perivascular in distribution. Hematoxylin and eosin stain. × 120.

thrombus that only partially obstructed it. The intimal surface of both renal arteries was smooth and showed no changes. The orifice of the celiac artery was completely obliterated while that of the superior mesenteric artery was narrowed. The origin of the inferior mesenteric artery was unaffected. A localized cylindrical dilatation about 2 cm. long, of the innominate artery, was present 1 cm. from its origin. The intima of the artery at this site was raised and thickened, without any ulceration or thrombi on its surface. Elsewhere in the innominate artery and also in the left common carotid and left subclavian were a few flecks of atheroma. The coronary arteries were patent and the intima smooth except for a few atheromatous flecks on the intimal surface of the right coronary.

The right kidney was slightly smaller than the left. The capsules stripped easily, the surfaces being smooth except for a moderately large wedge-shaped depressed scar on the posterior surface of the right kidney. The cut surfaces revealed normal calyces.

The lungs, liver, and spleen were congested. The brain was edematous and pale; over the dorsal surfaces of the occipital poles of both cerebral hemispheres in the subdural space were some old blood clots that caused a yellow staining of the underlying brain tissue. There was no hemorrhage into the brain substance and the cerebral arteries were normal.

Histologic examination of sections of the left ventricle revealed hyperplasia and hypertrophy of the muscle fibers. A small adherent thrombus was present on the endocardial surface below the aortic valve. There was no thickening of the endocardium or evidence of inflammation or fibrosis of the myocardium. In the abdominal aorta, at the level of the renal arteries, were irregular areas of intimal thickening due to fibroblastic proliferation together with deposition of homogeneous hyaline substance with some "lipid" clefts in the subintimal layer. There was ulceration of the surface of the intima with thrombi formation and organization of some of the thrombi. Patchy destruction of the elastic tissue of the media (fig. 8) had occurred and increased vascularity with infiltration by some lymphocytes and plasma cells was evident. The adventitia was thickened and showed an increased number of capillaries with round-cell infiltration. Sections of the innominate artery (fig. 9) exhibited similar changes except that there was no ulceration of the intimal surface. The walls of the renal arteries were normal except for a minimal round-cell infiltration of the right renal artery, which was probably a nonspecific reaction to the extensive thrombosis of this artery.

There was a large area of infarction in the right kidney (fig. 10) showing coagulation necrosis and marginal hemorrhage together with similar smaller areas. The rest of the kidney tissue and sections of the left kidney revealed no abnormality of the intrarenal vessels or renal parenchyma.

DISCUSSION

Both these children presented clinical problems as to the cause of their hypertension. The possibility of glomerulonephritis was consid-

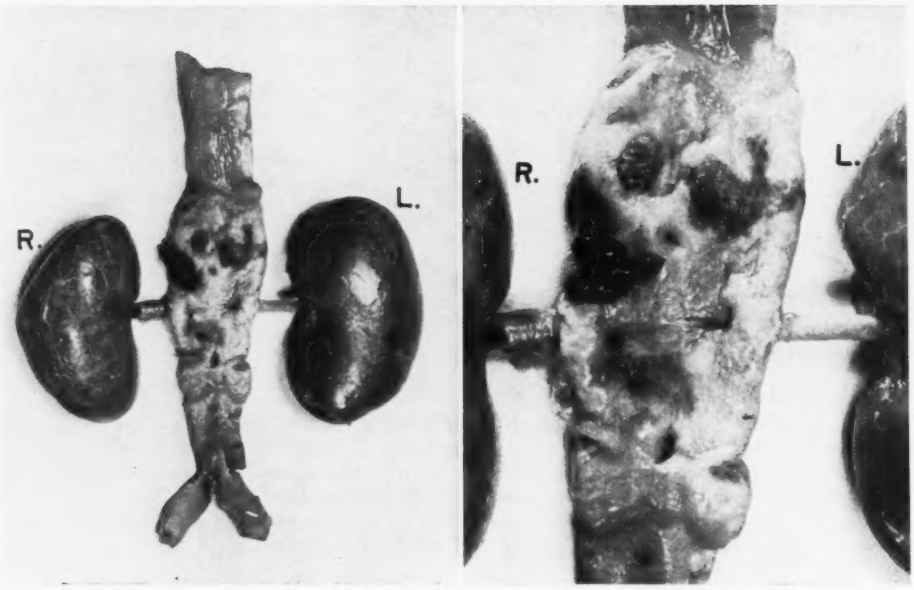

FIG. 6 *Left.* Case 2. Abdominal aorta with plaque and kidneys, the right being smaller than the left.

FIG. 7 *Right.* Case 2. Affected portion of abdominal aorta, slightly dilated, and intima thickened with thrombi on the surface. Orifice of right renal artery occluded by a thrombus that extends into the lumen of the artery giving it a swollen appearance as compared with the left. The orifice of the left renal artery is narrowed to a slit by the adjacent thickened and puckered intima.

ered in the first case, but excluded when it was observed that hypertension persisted in spite of the disappearance of initial albuminuria. No special investigations were done because of the severe state of cardiac failure, and the true nature of the disease was revealed only at necropsy. In the second case, the negative Regitine test, the lack of a demonstrable lesion by intravenous pyelography, and the clinical resemblance to the previous patient suggested similar lesions of the renal arteries, but death occurred before aortography could be done. There were no significant clinical or urinary findings to suggest the correct diagnosis in either patient, indicating the need for aortography in children in whom the cause of hypertension is obscure. Early diagnosis and treatment are essential, for hypertension is severe, death resulting from cardiac failure or intracranial hemorrhage.

The essential pathologic lesion in each patient was a panarteritis affecting a localized area of the abdominal aorta and resulting in stenosis of the visceral arteries (celiac, superior mesenteric, and renal) arising from the aorta at this level. Destruction of the media was extensive and in the second patient had caused dilatation of the involved portions of the aorta and innominate artery. The marked intimal hyperplasia, with thrombosis, was probably secondary to the changes in the media. There was no evidence of renal parenchymal disease and the absence of any arteriolar lesions in either kidney suggested that they had been protected from the impact of the hypertension by the occlusion of the renal arteries. In the absence at necropsy of any other ascertainable cause for the hypertension, it is safe to assume that the rise of blood pressure was due to partial obstruction of arterial blood flow to both kidneys, produc-

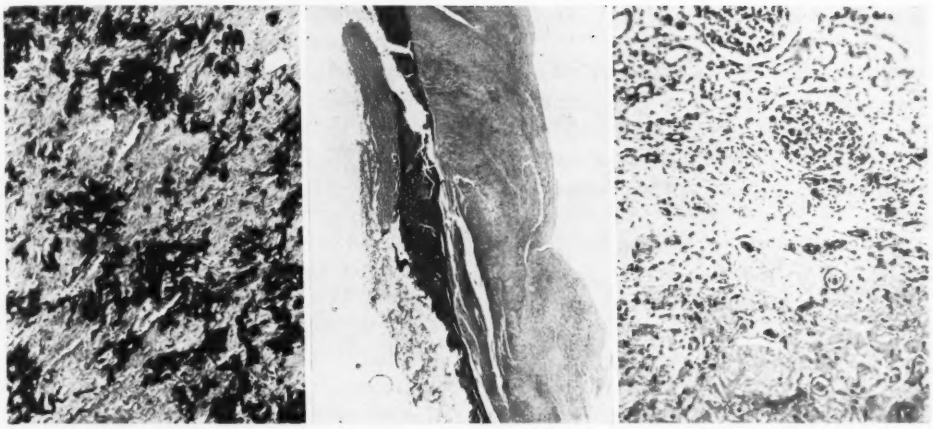

FIG. 8 *Left.* Case 2. Patchy destruction of media in abdominal aorta. Verhoeff-van Gieson stain. × 120.

FIG. 9 *Middle.* Case 2. Innominate artery: considerable swelling of intima, areas of destruction in media and adventitial thickening. Verhoeff-van Gieson stain. × 25.

FIG. 10 *Right.* Case 2. Right kidney. Area of infarction with normal renal tissue above it. Hematoxylin and eosin stain. × 135.

ing a clinical equivalent of the "Goldblatt kidney."

Reports of bilateral stenosis of the renal arteries with resultant hypertension are rare. Most of the cases have occurred in older adults, the commonest lesion being atherosclerosis of the abdominal aorta with occlusion of the renal artery orifices by atheromatous plaques or an aortic thrombus.[7–12] Endarterectomy done in some of these cases resulted in a fall of blood pressure. Other lesions have sometimes been encountered in relatively younger age groups: renal arteritis due to syphilis in a 24-year-old woman,[13] nodules of hyperplastic intima occluding the renal artery orifices in a 27-year-old woman,[14] and a thromboaortic plaque superimposed on an undetermined meso-aortitis in a 32-year-old woman.[15] In the last 2 patients, the pathologic lesions were localized to the abdominal aorta at the level of the origin of the renal arteries.

Hypertensive disease in childhood due to stenosis of both renal arteries has been only rarely recorded. In a male infant who died of hypertensive cardiac failure, Dawson and Nabarro[16] found narrowing of the renal arteries due to intimal hyperplasia; similar histologic changes were found in the coronary arteries and the authors suggested that the condition may have been one of healed polyarteritis nodosa. In a boy aged 14 years, who died of cerebral hemorrhage, Fisher and Corcoran[17] noted severe stenosis of the orifices of both renal arteries, the superior mesenteric artery, and the celiac artery caused by changes in the abdominal aorta consisting of fibrous proliferation of the intima with islands of lipophage infiltration. Poutasse and others[18] demonstrated, by aortography, stenosis of the origins of both renal arteries in a 15-year-old boy with hypertension. Histologic examination of the renal arteries, which were excised and replaced by arterial grafts, showed narrowing of the lumen by fibrous intimal hyperplasia: the blood pressure became normal following the operation.

The pathologic lesions found in the cases recorded above are not comparable to those found in the 2 children reported in this paper in whom the segmental distribution suggested an infective embolic process. No foci of sepsis were found at necropsy, however, and no organisms were demonstrated in sections of the affected portions of the vessels. Syphilis was considered, but the age of the patients, the negative serologic test (in case 2), and the gross appearance of the lesions, which were

focal rather than diffuse, excluded this possibility.

The lesions, however, bear a striking resemblance to those described as occurring in a now more widely recognized clinicopathologic entity of unknown etiology called variously pulseless disease,[19, 20] Takayashu's syndrome,[21, 22] obliterative brachiocephalic arteritis,[23] branchial arteritis,[24] aortic arch arteritis,[25] or primary arteritis of the aortic arch.[26] The essential lesion in this group of cases is a chronic progressive panarteritis of the aorta and the proximal segments of the arteries arising from the arch resulting in partial or complete thrombotic obliteration of their lumen. Although classically the arteritis is limited to the aortic arch, reports indicate that the descending thoracic[27] and abdominal aorta[22, 28] may also be affected. It is therefore possible, in primary arteritis of the aorta, for the proximal segments of the visceral branches, such as the coronary,[26] the mesenteric,[28] and the renal arteries,[22] to be involved in the pathologic process. The clinical presentation in such patients would therefore differ from the more usual one resulting from obstruction of the common carotid arteries. In a 40-year-old woman who had been observed as a case of Takayashu's syndrome by Ask-Upmark and Fajers[22] for many years, death occurred from uremia due to thrombotic obstruction of the aortic origins of the renal arteries resulting in a reduced blood supply to the kidneys. Histologic examination revealed a panarteritis with secondary arteriosclerotic changes involving the entire aorta, while the proximal portions of the branches of the aortic arch showed a similar type of arteritis with thrombotic occlusion of their lumina. The unusual location of the aortitis at the level of the origin of the renal arteries in the 2 patients reported in this paper resulted in the atypical presentation of renal hypertension. The adjoining visceral branches of the aorta, viz., the celiac and superior mesenteric arteries were also occluded.

The successful surgical treatment of hypertension due to obstructive lesions of both renal arteries[18] makes diagnosis important but this is difficult because urinalysis, rena function studies, and intravenous and retro grade pyelography are frequently normal, a stressed by Poutasse and Dustan[10] and De Camp and Birchall.[5] These authors, there fore, consider abdominal aortography essentia for the diagnosis of renal arterial lesions an indicated in all young patients with no family history of and no apparent cause for hyper tension. The diagnosis of "essential hyperten sion" in children, made in some instances i the past,[29, 30] would not be tenable unless ade quate renal arterial flow was demonstrated by this investigation.

Summary

In 2 children with hypertension, necropsy revealed a localized arteritis of the abdominal aorta that had resulted in occlusion of the renal artery orifices to produce the clinical equivalent of the "Goldblatt kidney." The histologic appearance of panarteritis suggests the possibility that these cases are variants of the disease called primary arteritis of the aortic arch or Takayashu's syndrome. The importance of diagnosis by means of aortography in view of possible surgical cure is stressed.

Acknowledgment

We are indebted to Dr. T. Balasingham, Department of Pathology, University of Malaya, Singapore, for performing the necropsy on case 2, and to Mr. V. Nalpon and Mr. Ho Tat Seng for the photographs.

Summario in Interlingua

In 2 patientes pediatric con hypertension, le necropsia revelava un aortitis localisate del aorta abdominal que habeva resultate in occlusion del orificios reno-arterial e le production del equivalente clinic de "ren de Goldblatt." Le apparentia histologic de panarteritis suggere le possibilitate e que iste casos representa variantes del morbo designate como arteritis primari del arco aortic o syndrome de Takayashu. Es signalate le importantia de establir le diagnose per medio de aortographia con le objectivo de effectuar possibilemente un curation chirurgic.

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Serum-Induced Thrombosis

Studies of its Induction and Evolution Under Controlled Conditions in Vivo

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A simple, reproducible, physiologic technic is delineated for the production and study of thromboembolism. The method is based on the observation that the infusion of serum, in striking contrast to plasma, induces massive thrombosis in vascular segments containing stagnant blood far removed from the site of infusion. Data are presented on the nature of the thrombosis-inducing activity of canine and human serum, on the effect of serum infusions on recipient animals, and on the morphology of the induced thrombus. The adaptability of this method to the study of a variety of thromboembolic phenomena in man is described.

CLINICAL approaches to thromboembolic phenomena have thus far been hampered by the lack of adequate criteria for recognizing the incipient or active thrombotic state.[1, 2] Pathologic observations have in turn been limited by the inability to assess accurately the age of thrombi and to determine, in many instances, whether clots found at necropsy were formed ante mortem.[2] Clinical-pathologic correlations have frequently been unrewarding because of the inability to determine the extent to which thrombi fracture, dissolve, or propagate between the onset of the clinical episode and the time of pathologic examination.

Numerous experimental technics have been devised to produce thrombosis or vascular obstruction in animals. Some methods have depended on the production of marked intimal damage by mechanical, chemical, or electrical injury.[3-16] Others have been based on the injection of thromboplastin,[17-20] or thrombin.[10, 21, 22] Still others have utilized the infusion of extracorporeally formed fibrin,[23, 24] whole blood clot,[25-31] or particulate foreign matter,[32-41] and several investigators have incorporated into the clot radioactive[21, 42] or radiopaque[20] substances for subsequent identification of the thrombus or embolus. Many of these technics have been extremely unphysiologic, and were initially designed to study 1 or 2 aspects of thromboembolism. In almost all the procedures, the production of clot has been variable, and the ability to control or predict its size and shape has been limited. Data concerning the initial histopathology have frequently been meager and information concerning clot initiation, propagation, and embolization has been restricted by the nature of the technics themselves.

In the absence of an adequate clinical or laboratory test for intravascular thrombosis, a versatile experimental technic of thrombus formation would aid in evaluating discrepancies between clinical and pathologic aspects of thromboembolic phenomena and in correlating knowledge of the coagulation and lytic systems in vivo. Stimulated by the observations of Glenard[43] and Baumgarten[44] concerning the prolonged fluidity of a stationary column of blood in a vein occluded between 2 carefully applied ligatures, we at first studied the early changes in coagulation within isolated segments of the jugular veins of dogs

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Although coagulation proceeded in this system, it was slow and incomplete for as long as 8 hours after the vein was isolated.[45] An attempt was made, therefore, to accelerate coagulation by as physiologic an agent as possible without producing defibrination, seriously injuring the endothelium, or injecting extracorporeally formed clot. Serum, a natural product of the coagulation process itself, was selected for this purpose because it possesses clot-promoting activity in vitro[46-48] and has been successfully used as a blood substitute in man.[49] Moreover, Hayem[50] and subsequently Feissly[51] had demonstrated that serum could induce a clot in vivo.

It is the purpose of this report to describe this technic and to present some of the results that have derived from its use.

Method

The basic technic, as used in dogs, has been described previously.[52] The animal is anesthetized with sodium pentobarbital, a segment of jugular vein 1 or more centimeters in length is freed from its surrounding tissues and its tributaries are ligated. Thirty milliliters of heterologous canine serum eluate,* independent of the weight of the animal, are then infused into an antecubital vein in 30 seconds. Within 60 seconds after the completion of the infusion, the previously freed jugular vein segment is gently isolated with seraffine clamps. A thrombus forming a cast of the occluded vein segment appears within several minutes after clamping (fig. 1). Thrombi also invariably form behind the distal occluding clamp. Stasis in this area is partial, since blood flow in the region of these thrombi continues by way of patent collateral venous tributaries and the fully patent distal continuity of the vein itself. Partial narrowing of the vein prior to the infusion of the serum eluate also produces thrombi distal to the narrowed zone.[52]

A similar and more quantitative technic has also been developed for the infusion of human serum into rabbits.[53] Human serum (1.32 ml. per Kg. of rabbit diluted with physiologic saline to a constant volume) is injected in 15 seconds into a contralateral rabbit ear vein. Within 15 seconds after completion of the infusion, the previously freed jugular segment is isolated. When, 10 minutes later, the isolated vein segment is opened, a clot forming a cast of the vessel is found.

*Preparation of this eluate has been previously described in detail.[52]

Fresh thrombi formed in vessels occluded following the infusion of serum or serum eluate are not adherent and are readily moved by the stream of fluid blood when the obstructing clamps are removed. By this means, in the dog, emboli have been released to the portal venous bed, the tibial arteries, and the pulmonary arteries. By applying simultaneous stasis to various vascular systems after the infusion of serum, multiple thrombi of the same histologic composition can be produced in different areas of the circulation at the same time. In certain areas, such as the femoral or jugular veins, comparable simultaneous thrombi have been formed bilaterally, permitting release of 1 thrombus as an embolus while the contralateral thrombus is maintained in situ as a control. When large amounts of thrombi are desired, the infusion and clamping may be repeated as often as every 10 minutes; in this fashion a large volume of thrombi may be sent to a specific vascular area such as the lung. In addition to releasing varying amounts of freshly formed thrombi, it is also possible to permit thrombi to age in situ, thereby undergoing varying degrees of alteration for hours or days prior to their release.

Although complete absence of endothelial injury at the site of thrombus formation is difficult to establish,[54] a variety of experiments has demonstrated that vascular obstruction per se does not cause endothelial damage sufficient to produce thrombosis by the method used.[52] In any event, the release of thrombi to distant vascular areas, such as the pulmonary arteries, permits study of the response of previously uninjured vessel wall to the presence of the contained thrombus.

Thrombi were prepared for microscopic study by fixation in 10 per cent formalin in isotonic saline, and sections were stained with hematoxylin and eosin. A few thrombi were also fixed in hypotonic solutions, such as 5 per cent and 10 per cent aqueous formalin.

Tidal volume, minute volume, and rate of respiration were recorded on a kymograph attached to a Tissot spirometer. Arterial blood pH was measured with a Radiometer glass electrode. The carbon dioxide content and the oxygen content and capacity of arterial blood were measured by the technic of Van Slyke and Neill.[55] The arterial carbon dioxide tension was measured by applying the arterial pH and plasma carbon dioxide content to the line chart of Van Slyke and Sendroy.[56] After collection of the expired air in a Douglas bag, oxygen consumption and carbon dioxide production were measured in a 0.5-ml. Scholander apparatus.[57] The right ventricle was catheterized through the right external jugular vein. Electrocardiographic tracings and right ventricular pres-

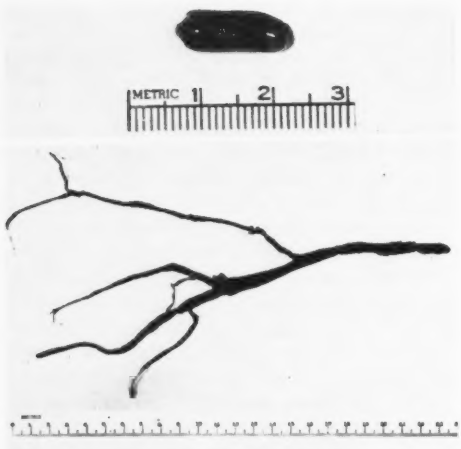


FIG. 1 *Top.* Photograph of typical thrombus produced in jugular vein of dog 10 minutes after serum infusion.

FIG. 2 *Bottom.* Photograph of a thrombus distal to a single clamp placed on the femoral vein of a dog and removed 10 minutes after serum infusion.

sures, with a Statham strain-gage, were obtained on a multichannel direct-writing recorder.

Platelet counts were performed by the method of Rees and Ecker;[58] clotting times by the method of Lee and White;[59] thromboplastin generation by the method of Biggs and Douglas;[60] 1-stage prothrombic activity by the method of Rosenfield and Tuft;[61] prothrombin, factor V and factor VII activities by the methods of Owren;[62, 63] and "Stuart" factor activity by the method of Bachmann, Duckert, and Koller.[64] Platelet-poor plasma was prepared by the method of Brinkhaus.[65]

RESULTS

Single infusions of 30 ml. of canine serum eluate into a series of 200 dogs resulted in thrombi forming a complete cast of the isolated vein lumen in 198 animals. When veins were clamped without prior infusion of serum eluate, no macroscopic clot was observed for periods ranging from 20 to 90 minutes after clamping. Following infusion of serum eluate on the other hand, visible clot developed within 60 seconds after the vein was isolated. The thrombus increased rapidly in size and, after 5 minutes, formed a complete cast of the isolated segment. A high degree of reproducibility could also be demonstrated with the infusion of human serum into rabbits; thrombi were formed in the jugula veins of 23 of 24 animals following seru infusion. The thrombosis-inducing activity serum was transient. Under the experiment conditions used, a delay of 2 to 10 minut in the dog and 30 to 60 seconds in the rabb between infusion and clamping the vei segment resulted in variable-sized thromb With greater delays, no thrombi formed.

The size and shape of the thrombus a determined by the caliber of the vessel an the length of the isolated segment. Thu single clots varying from 0.5 to 15 cm. i length and from 0.1 to 0.8 cm. in diamet have been produced in the dog. The occlu sion of a vein by a single clamp produc variable lengths of clot, often as great as 3 to 40 cm. (fig. 2).

The location of the thrombi is determine by the sites of vessel isolation. Thrombi o predetermined size can thus be formed in th femoral, renal, and portal veins, as well as in the jugular venous system. In similar fashion, thrombi can be induced in th femoral, renal, coronary (fig. 3), and carotid arteries. In addition, thrombi can also be formed in the inferior vena cava, the abdominal aorta (fig. 4), and the atrial appendages (fig. 5).

Nature of the Thrombosis-Inducing Activity of Serum

In contrast to the formation of thrombi following infusions of canine serum or serum eluate in dogs, infusion of 100 ml. of physiologic saline solution into each of 5 dogs, 100 ml. of distilled water into each of 5 additional dogs, and 100 ml. of carefully collected plasma into another group of 10 animals, failed to induce thrombus formation in the standard test system.

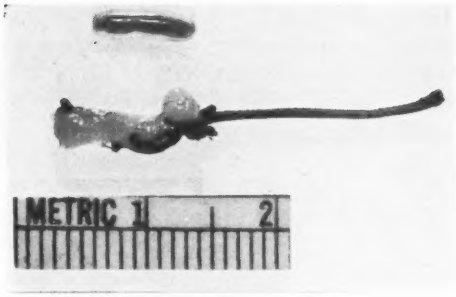
Thrombi have been repeatedly induced not only in the dog and rabbit, but also in the guinea pig by infusions of homologous and heterologous serum of each species respectively, and by human serum. Thrombi in both the dog and rabbit have in addition been produced by the infusion of sera from cow, lamb, and pig.

As noted above, 23 of 24 rabbits receiving 32 ml. of normal human serum per Kg. eveloped thrombi forming a cast of the iso- ted jugular vein segment. Sixteen of 23 abbits receiving 1.32 ml. of normal platelet- ich recalcified human plasma formed com- arable thrombi. Thrombi also formed when latelet-poor recalcified plasma was used as he infusate. In sharp contrast, human plasma ollected in the cold with siliconized equip- nent[53] completely failed to induce thrombo- is in rabbits. Thus, 20 infusions of normal uman plasma (1 part 0.1 M sodium oxalate o 9 parts of whole blood) at a dose of 1.32 ml. per Kg. and 10 infusions at twice this standard dose did not cause thrombosis. Human plasma collected with 1 part of 3.2 per cent sodium citrate to 9 parts of whole blood, or with 1 part of a 10 per cent solu- tion of the disodium salt of ethylenediamine- tetraacetic acid to 9 parts of whole blood, also failed to induce thrombi. Unless plasma is processed according to the prescribed technic, partial and occasionally comblete thrombus formation may occur. Plasma less care- fully collected, although reflecting the pres- ence of the thrombosis-inducing activity of serum, nevertheless showed normal thrombo- plastin generation, normal prothrombic ac- tivity, and normal prothrombin, factor V, factor VII, and "Stuart" activities.

The thrombosis-inducing activity of normal human serum is destroyed at 4 C. for 96 hours, but is retained for weeks at −20 C. The active moiety is completely adsorbed on barium sulfate and recovered from the ad- sorbate by elution with citrate.

Systemic Response of Recipient Animal to Serum and Serum Eluate Infusions

In 14 dogs the infusion of heterologous canine serum eluate produced in the recipient animal no significant alteration in body tem- perature, tidal volume, minute volume or rate of respiration, arterial blood pH, arterial carbon dioxide content or tension, arterial oxygen content or capacity, oxygen consump- tion, or carbon dioxide production. There were also no changes in cardiac rate, rhythm,



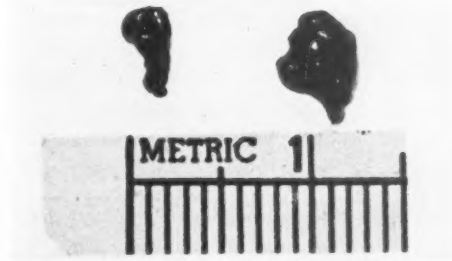


FIG. 3 *Top.* Photograph of thrombus and segment of coronary artery of dog in which it was formed after serum infusion.

FIG. 4 *Middle.* Photograph of thrombus and segment of abdominal aorta of dog in which it was formed after serum infusion. *Arrows,* location of clamps placed on aorta immediately after infusion.

FIG. 5 *Bottom.* Photograph of thrombi formed in left atrial appendage of dog after serum infusion.

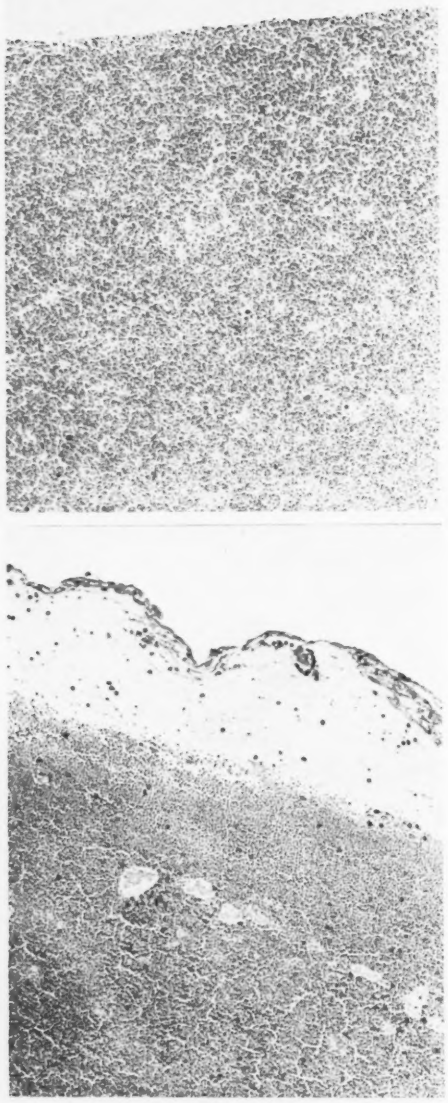


FIG. 6 *Top.* Photomicrograph of 10-minute, complete stasis clot formed in jugular vein of dog. × 128. Note absence of lines of Zahn.

FIG. 7 *Bottom.* Photomicrograph of 10-minute, complete stasis clot formed in jugular vein of dog and fixed in hypotonic 10 per cent aqueous formalin. × 128. Note fibrin mesh in areas of red cell lysis at surface.

electrocardiographic configuration, or right ventricular pressure.

In 8 dogs infused with heterologous canine serum and in 6 rabbits infused with normal human serum, neither thrombocytopenia nor visible hemolysis of the plasma was observed in blood samples obtained from the recipient animals 30 seconds, 5, and 30 minutes after infusion of serum or serum eluate.

The clotting time of the recipient animal in untreated and in siliconized glass tubes was transiently but significantly decreased immediately following serum infusion. There was also a marked impairment in thromboplastin generation, but the 1-stage prothrombic activity, prothrombin, and convertin concentrations remained normal.

Whereas the infusion of serum via a peripheral vein invariably induced thrombus formation in any vessel where blood flow was retarded, the infusion of the same amount of normal human serum into the portal vein of 8 rabbits failed to induce thrombus formation in a systemic vein. In 4 animals thrombi were successfully induced in systemic veins by an infusion of serum into the marginal ear vein before and after an unsuccessful portal vein infusion.

Morphology of the Serum-Induced Thrombus

Thrombi from 31 dogs were examined 10 minutes to 24 hours after their formation. The thrombi formed under conditions of complete stasis were red, smooth, firm, flexible, complete casts of the isolated vein segments. Microscopic examination revealed a fine meshwork of fibrin in which red cells were trapped (fig. 6). The erythrocytes were sharply defined, densely packed, often in rouleaux formation; white cells were distributed at random. The fibrin strands were usually difficult to see among the densely packed red cells, but became readily apparent when the peripheral erythrocytes had been partially laked by hypotonic fixatives such as 10 per cent aqueous formalin (fig. 7). Small hyaline foci from which fine fibrin strands appeared to radiate, and around which a thin

llar of leukocytes was occasionally noted, ere scattered through the clot; these apparitly consisted of centers of fibrin formation nd possibly platelets. These hyaline foci also ecame more evident when the red cells had een partially laked (fig. 7). There was o evidence, however, of the anastomosing trands rich in platelet material (the ines of Zahn) generally associated with hrombi formed at sites of endothelial injury. Significant variation in gross or microscopic ppearance was not noted when such thrombi vere examined after periods ranging from 20 minutes to 4 hours from the time of formation.

The complete stasis thrombus showed no essential difference from the red clot produced by withdrawing blood from the animal and allowing it to clot in vitro or from postmortem clot removed from the chambers of the left side of the heart after the death of the animal.

Thrombi formed under conditions of partial stasis behind the distal occluding clamp were frequently bizarre in shape, varied greatly in length, and usually failed to form complete casts of the venous lumen. Side-arm extensions corresponding to connecting venous tributaries were often seen. Grossly, a small amount of gray-white surface accretion was noted on some of these thrombi, more frequently on the distal "tail" of the thrombus or on the side-arm extensions. Microscopic examination revealed that these thrombi were similar in all respects to those formed by complete stasis except for variable amounts of fibrin, leukocytes, and hyaline platelet material on the surface corresponding to the accretion noted grossly. Only minute amounts of this material were noted after 20 minutes, but it became increasingly evident on the surface of most thrombi followed in situ for periods up to 4 hours or longer.

Complete stasis thrombi released to areas of narrowing in more proximal portions of the vein also tended to show this accretion in the majority of instances up to periods of 4 hours and invariably after 24 hours. The same was true of such thrombi released into the systemic circulation and recovered from the right ventricle or pulmonary arteries after periods of 20 minutes or longer; the amount of such accretion on emboli tended to be greater than on thrombi of comparable age confined to the vein of origin (fig. 8). The accretion appeared morphologically identical to the material comprising the lines of Zahn in human thrombi and was usually limited to zones at or near the surface of the thrombus. In some instances, however, narrow zones could be observed extending for variable distances between clot laminations as though layers had been formed at different times (fig. 9). On the other hand, no evidence of accretion, either on the surface or between the layers of thrombus could be observed on postmortem clot or in clot permitted to form in vitro.

Discussion

The method described in this communication affords a simple, reproducible, physiologic technic whereby one or more thrombi of uniform composition and predetermined size can be produced in any selected vessel without significant systemic side effects. These thrombi may be produced in a variety of experimental animals and can be studied in situ or released to vascular beds initially free of endothelial injury. With this technic observations can be made on factors relating to the initiation, propagation, dissemination, and dissolution of intravascular thrombi.

The lack of significant systemic side effects from the infusion of serum suggests that the thrombotic activity of serum acts through a specific pathway upon the coagulation mechanism of the recipient animal rather than through other physiologic alterations.

The identity of the thrombosis-inducing activity of human serum remains obscure, but it is not an artifact. It arises, directly or indirectly, as a consequence of the coagulation process itself, has been demonstrated in platelet-poor recalcified plasma, and is distinct from tissue thromboplastin,[52] thrombin,[52, 53] factor V (ac-globulin), factor VII

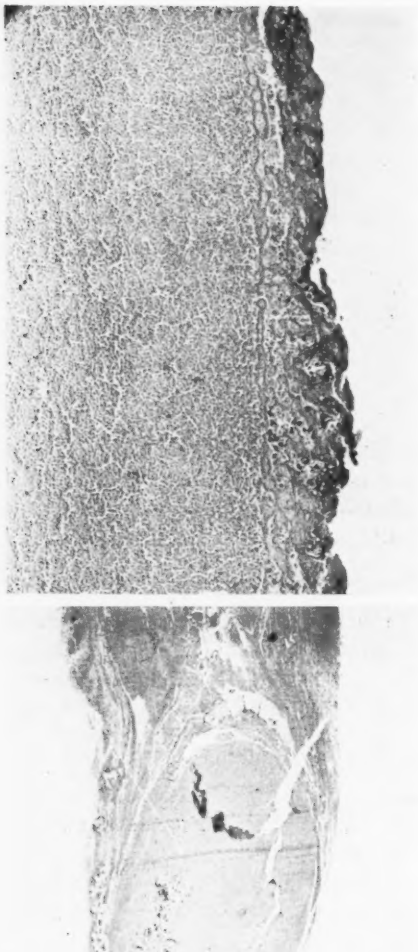


FIG. 8 *Top.* Photomicrograph of clot released to lung and recovered 10 minutes later. × 128. Note heavy surface accretion of fibrin, leukocytes, and platelet material.

FIG. 9 *Bottom.* Photomicrograph of clot released to proximal area of narrowing and removed 70 minutes after formation. × 10. Note "tail" and coating of accretion with inclusion into clot to resemble lines of Zahn.

(convertin), factor VIII (antihemophilic glob ulin), and "Stuart" factor.[66] On the othe hand, it is related to at least 3 specifi clotting factors essential for the firs phase of coagulation: factor IX (plasm thromboplastin component, PTC), Hagema factor, and plasma thromboplastin antec dent (PTA).[66] It is possible that the initia tion of experimental thrombosis with huma serum may be dependent on the presence c these factors in "activated" form, or on th formation of the complex termed "intrinsi thromboplastin." The failure to produce sy temic thrombi when serum was infuse through the portal vein[7] suggests that thi thrombotic moiety is inactivated in the liver.

The level of the thrombosis-inducing ac tivity in normal human serum can be deter mined quantitatively by a bioassay based o a direct relation between in vivo thrombosis i rabbits and the quantity of serum infused.[5] This assay of human serum thrombosis inducing activity may eventually serve as a guide to its isolation, purification, and char acterization.

Morphologic studies of the thrombi pro duced by this method indicate that they are in no way distinguishable from postmortem or in vitro clots when stasis is complete. When stasis is partial, however, or when the throm bus is exposed to rapid blood flow, as in passage to the lung, variable amounts of eosinophilic hyaline accretion of fibrin, leuko cytes, and platelets accumulate on the sur face, apparently in direct relation to the amount and duration of blood flow. Such accretion may, in fact, be included in the substance of the thrombus as it propagates, eventually becoming indistinguishable from the lines of Zahn. This sequence is an estab lished mechanism in the instance of a throm bus propagating from the white platelet nidus formed at a site of endothelial in jury.[67-69] It would appear that, in the dog at least, a similar sequence may be initiated by a red, serum-induced, stasis thrombus formed in areas of retarded flow where endothelial injury is absent or so minimal that thrombus

ormation will not form in the absence of rum infusion.[52]

No species specificity to the serum ifused, or to the recipient animal has yet een found. This uniformity of response uggests that thrombosis resembling the exerimental serum-induced complete stasis hrombus may be initiated in areas of rearded blood flow free of endothelial damage nder appropriate conditions in man. Such hrombi, hours after their formation, might e difficult to distinguish from thrombi origmating as a platelet nidus at a site of local ndothelial injury. Although no evidence has yet been uncovered demonstrating that the mechanism of serum-induced thrombosis has a counterpart in man, sufficient data have been accumulated to encourage further investigation of such a hypothesis.

The technic of serum-induced thrombosis, in our hands as well as in those of others, has provided data on the response of the intact animal to peripheral arterial,[70, 71] coronary arterial,[72] and pulmonary arterial emboli,[73] in addition to observations concerning the effectiveness of anticoagulant[74, 75] and lytic[71, 72, 76] agents. Finally, a standard method of thrombus induction has been developed that may prove extremely helpful in clarifying some of the conflicting results obtained by different laboratories studying experimentally various aspects of thromboembolic disease.

Summary

A method of serum-induced thrombosis has been described whereby thrombi of predetermined size can be formed in 1 or more vascular beds singly or sequentially.

The thrombosis-inducing activity is present in platelet-poor recalcified plasma as well as in serum, but is absent, in an active form, from carefully collected normal plasma. The thrombotic activity arises, directly or indirectly, as a result of the coagulation process itself and is not species specific.

The red, serum-induced thrombus cannot be distinguished from in vitro or postmortem clot at the time of its formation. When exposed to flowing blood, however, a surface accretion of fibrin, leukocytes, and platelet material forms that is similar in appearance to the lines of Zahn. The extent of this accretion is in direct relation to the amount and duration of blood flow.

In addition to providing a versatile technic for experimental study of thromboembolism, the observations herein reported indicate that thrombi produced by this method may eventually become indistinguishable from those arising at sites of endothelial injury. The accumulated data raise the possibility that a similar mechanism of serum-induced thrombosis may be operative in man.

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Summario in Interlingua

Es describite un methodo pro le induction de thrombose per sero, permittente le formation de thrombos de dimensiones predeterminate in un o plure vasculaturas, individualo sequentialmente.

Le activitate thrombopoietic es presente in sero e etiam in plasma recalcificate que es povre in plachettas, sed illo es absente in cautemente collectionate plasma normal. Le activitate thrombotic se manifesta, directe- o indirectemente, como resultato del processo coagulatori mesme e non es specific al specie.

Le thrombo rubie que es inducite per sero non pote esser distinguite al tempore de su formation ab un coagulo formate in vitro o post morte. Tamen, quando illo es exponite al effecto de sanguine currente, illo disveloppa un accretion superficial de fibrina, leucocytos, e plachettas. Iste accretion exhibi un apparentia simile al lineas de Zahn. Le magnitude de illo es relationate directemente al quantitate e al duration del fluxo de sanguine.

Le hic-reportate observationes provide un technica versatile pro le studio experimental de thromboembolismo. Illos indica que throm-

bos producite per iste methodo pote, in le curso del tempore, devenir indistinguibile ab thrombos formate in sitos de injuria endothelial. Le accumulate datos subleva le possibilitate que un simile mechanismo de induction de thrombose per sero es presente in le homine.

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A Simplified Indicator-Dilution Technic for the Localization of Left-to-Right Circulatory Shunts

An Experimental and Clinical Study of Intravenous Injection with Right Heart Sampling

By EUGENE BRAUNWALD, M.D., WILLIAM W. PFAFF, M.D., ROBERT T. L. LONG, M.D., AND ANDREW G. MORROW, M.D.

Indicator-dilution curves recorded from a systemic artery after injection in the right heart may show the presence of a left-to-right shunt but will not localize it. Injections into the left side of the heart with arterial sampling or into the pulmonary artery with right heart sampling provide accurate and sensitive methods for localization but the technics are inconvenient and sometimes impossible to apply. A simplified indicator method for the localization of left-to-right circulatory shunts is described.

INDICATOR-dilution curves are now a well-recognized and important method for the study of patients with congenital and acquired heart disease[1-3] and have been found of particular value in the diagnostic evaluation of patients with cardiac shunts. The detection and localization of right-to-left shunts by this means was described by Swan, Zapata-Diaz, and Wood in 1953[4] and remains an important application of indicator-dilution curves. The precise characterization of left-to-right shunts, however, has been somewhat more difficult.

When an indicator is rapidly injected into a peripheral vein, the right side of the heart, the pulmonary artery, or the left atrium of a patient with a left-to-right shunt, it is at first dispersed within the large volume of blood that traverses the central circulation. The indicator takes 2 circulatory paths in the left side of the heart: a portion of it follows the normal route to the systemic arterial bed while the remainder is shunted from the left to the right side of the heart, through the pulmonary circulation and returns to the left side. A fraction is then again shunted from left to right. The resulting dilution curve, recorded from a systemic artery, is characterized by a normal ascending limb, a relatively low peak concentration and a descending limb which is prolonged by recirculating indicator.[5, 6] As long as the indicator is injected proximal to the origin of the left-to-right shunt, varying the site of injection usually modifies the resultant curve only by compressing or expanding it as the volume of blood between the sites of injection and sampling varies. The basic contour as described above, however, remains unchanged. Indicator-dilution curves obtained by peripheral venous, right heart, or pulmonary artery injection with systemic arterial sampling are thus of value in the detection of a left-to-right cardiac shunt when it exceeds approximately 20 to 30 per cent of the pulmonary blood flow. Such curves have not been useful in the localization of left-to-right shunts except in the study of patients with partial anomalous pulmonary venous drainage.[7]

Reports from this clinic[8-11] and elsewhere[12, 13] have demonstrated that systemic arterial dilution curves recorded following injections into the chambers of the left side of the heart and aorta are of considerable value in this regard. When the injection is

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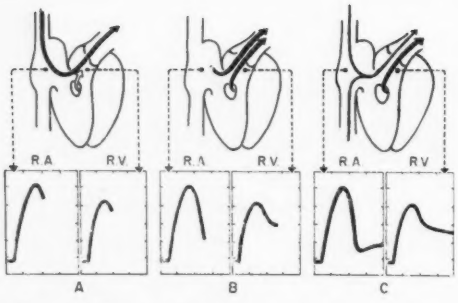

FIG. 1. Diagrammatic representation of the evolution of indicator-dilution curves obtained by venous injection, right atrial (*RA*) and right ventricular (*RV*) sampling in a patient with a left-to-right shunt through a ventricular septal defect. During its initial circulation (*A*) the indicator is diluted in the RV by shunted blood (*open arrow*) and the peak concentration in the RA exceeds that in the RV. When shunted indicator reaches the RV (*B*), it interrupts the descending limb of the RV but not the RA curve. Finally, in *C* the appearance of normally recirculating indicator interrupts the bottom of the descending limb of the RA curve while indicator continues to shunt into the RV.

made distal to the origin of the left-to-right shunt, all of the dye follows the normal circulatory path across the aortic valve and into the peripheral circulation. The resultant arterial dilution curve has a steep ascent, a slightly slower descent, and returns to the baseline before the appearance of recirculating indicator. However, when the injection is made proximal to the origin of the shunt, only a portion of the indicator takes the normal circulatory path. The remainder passes across the defect and through the pulmonary circulation. The late appearance of this portion of the indicator in the peripheral artery abruptly interrupts the descending limb of the curve and results in either a secondary peak or in an abrupt change in the slope of the descending limb. While this method has received considerable practical application, it has the disadvantage of requiring either direct left heart catheterization or passage of the catheter into the left side from the right.

Recently, the introduction of tricarbocyanine dye (cardiogreen) by Fox and collaborators[14] has made possible the recording of satisfactory dilution curves from the right side of the heart and pulmonary artery. Such curves have been utilized extensively by Wood and his associates for the localization of left-to-right cardiac shunts at the time of right heart catheterization.[2, 15] These investigators have usually injected the dye into the pulmonary artery while sampling from another catheter or from the proximal lumen of a double-lumen catheter at various sites up-stream (proximal) to the site of injection. The early appearance of dye in the right side of the heart signifies the presence of a left-to-right shunt, while the particular chamber in which the dye appears indicates the site of entry of the shunt. Our experience has confirmed the value of this technic in the detection and precise localization of even very small shunts. However, the insertion of 2 cardiac catheters or of a double-lumen catheter has, in our laboratory, often been found to be inconvenient or even impossible, particularly in infants and young children. The present report describes a simplified indicator method that obviates these difficulties.

When an indicator is rapidly injected into a peripheral vein of a patient without a left-to-right shunt, the dilution curve obtained by sampling blood from a vena cava, the right side of the heart, or the pulmonary artery is characterized by a rapid ascent and a smooth descent followed by the appearance of indicator which has recirculated normally through the systemic bed. A similar curve results when the site of sampling is proximal to the entry of a left-to-right shunt. However, when the site of sampling is down-stream (distal) to the entry of a shunt, the appearance in the right side of the heart of indicator which has been shunted from left-to-right interrupts the descending limb of the curve. This results either in a secondary peak or in a prolonged smooth descending limb. Thus, by alteration of the site of sampling within the venae cavae, right heart, and pulmonary artery the site of entry of the shunt may be correctly localized (fig. 1).

Materials and Methods

Atrial septal defects were created in 4 mongrel dogs by excising a portion of the atrial septum during a period of inflow occlusion. In 6 dogs ventricular septal defects were made by the method of Kay and Blalock.[16] A circular punch was introduced through the wall of the right ventricle and advanced through the interventricular septum. Suction was then applied to the instrument and a portion of the septum was removed. In 5 of these dogs varying degrees of tricuspid regurgitation were also produced, since either chordae tendineae or papillary muscles were severed by the punch. All 10 dogs were sacrificed and the presence of the defect was confirmed at postmortem examination.

A total of 24 patients have been studied to date. In 8 there was no clinical suspicion of a left-to-right shunt and this impression was confirmed in each by a negative nitrous oxide test[17] and at operation in 4. The remaining 16 patients had left-to-right shunts proved by this method. The diagnosis was further confirmed at open operation in 12 of these patients.

Cardiogreen dye[14] was employed as the indicator, 1.25 mg. of dye per ml. being contained in 1.0 to 2.5 ml. of saline solution. In the experimental studies the dye was injected into a cannula inserted in the femoral vein. In the patients the dye was injected either into an antecubital vein or into an indwelling Cournand needle in the femoral vein; the latter was found to be particularly convenient. Injections were made as rapidly as possible and were always completed in less than 1 second. Indicator-dilution curves were inscribed with either a direct-writing or a photographic recorder and a cuvette densitometer[18*] by withdrawing blood from the cardiac catheter with a motor-driven syringe at a rate of 20 ml. per minute. The catheters (no. 6F to no. 8F Cournand) ranged in volume from 0.64 to 1.23 ml. The volume of the tubing between the proximal end of the catheter and the densitometer was held constant at 0.41 ml. The volume of the cuvette in the densitometer is 0.30 ml. The response of the densitometer to a sudden change in density is 95 per cent in 1 second and 99 per cent in 2 seconds.[19] Since only the contours of the dilution curves were analyzed, the curves were not calibrated. In the patients and dogs with left-to-right shunts, curves were generally obtained by sampling both proximal and distal to the entry of the shunt. In patients without shunts generally only 1 curve was recorded from the pulmonary artery or the right side of the heart.

*Manufactured by the Gilford Corporation, Elyria, Ohio.

Results

In all 10 dogs the left-to-right shunt was detected; its site of entry was correctly localized in all but 1 instance. In this dog with an atrial septal defect, the dye curves obtained with both right atrial and inferior vena caval sampling were normal, while the curve from the right ventricle clearly showed the presence of a left-to-right shunt. It is believed that this error in localization was related to improper positioning of the catheter in the right atrium, so that it did not sample blood that had been shunted. This observation emphasizes the importance of sampling blood from as distal a site as possible in each chamber, e.g., in the right atrium near the tricuspid valve or in the outflow tract of the right ventricle.

The presence or absence of a left-to-right shunt was determined correctly in all 24 patients studied. In 4 patients the left-to-right shunts were relatively small with pulmonary/systemic flow ratios less than 1.3 as determined by the nitrous oxide test.[17] Representative curves obtained from patients and dogs are illustrated in figures 2 to 6.

Discussion

The practical advantages of the method described are that left heart catheterization, and the insertion of either 2 catheters or of a double-lumen one are obviated. By sampling both proximal and distal to the site of entry of the shunt each patient serves as his own control. Thus the contour of the dilution curve from the vena cava proximal to the entry of any shunt will be modified by the cardiac output and by the appearance of indicator recirculating normally through the systemic circuit. The latter often interrupts the bottom third of the descending limb. The vena caval curve may be compared with that obtained from the chamber which is distal to the site of entry of the suspected shunt. The indicator which has been shunted from left-to-right either greatly prolongs the descending limb (figs. 2 and 3) or abruptly interrupts its upper portion (figs. 4 and 5).

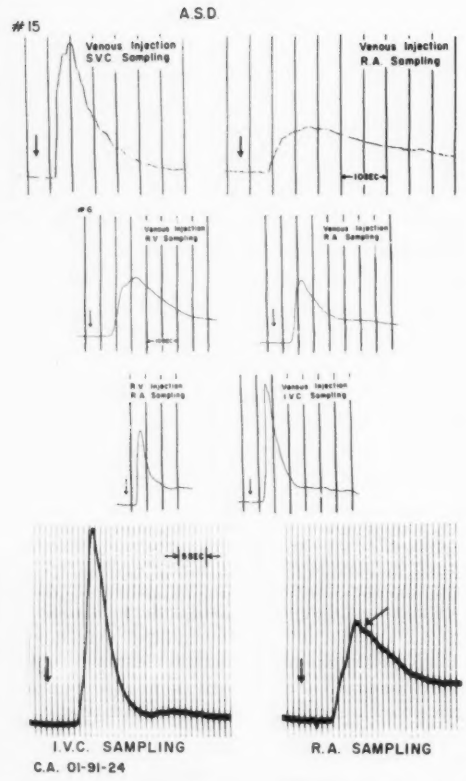

FIG. 2 *Top.* Dilution curves following peripheral venous injection of dye and sampling blood from the superior vena cava (*SVC*), and the right atrium (*RA*), of a dog with an atrial septal defect. Equivalent amounts of cardiogreen were injected and the sensitivity of the densitometer was held constant. The right atrial curve is characterized by a lower peak concentration and much longer descending limb than the vena caval curve. *Vertical arrows,* indicate instant of injection.

FIG. 3 *Middle.* Dilution curves in a dog with a ventricular septal defect and tricuspid regurgitation. Following femoral vein injection the control curve from the inferior vena cava (*IVC*) is normal. With right atrial (*RA*) sampling the descending limb is somewhat slowed and the right ventricular (*RV*) curve is grossly distorted. This indicates that a small left-to-right shunt enters the right atrium and a larger shunt enters the right ventricle. The presence of tricuspid regurgitation is proved by the immediate appearance of dye in the RA following its injection into the RV.

FIG. 4 *Bottom.* Dilution curves following femoral vein injection in a patient in whom the presence of a large atrial septal defect was proved at open operation. The control curve from the inferior vena cava (*left*) is normal. *Oblique arrow,* high on the descending limb of the right atrial curve, indicates the presence of recirculating dye and thus the presence of a left-to-right shunt at the atrial level.

A gross approximation of the magnitude of the shunt may be achieved by noting the difference between the curves obtained from proximal with those obtained from distal to the entry of the shunt. It is pertinent that even shunts of small magnitude could be accurately detected.

The well-recognized fact that blood sampled from a vena cava or from the right atrium is not completely mixed[10, 17, 20] limits the precision of shunt localization of the method described in a manner somewhat analogous to the oxygen method.[20] However, the latter depends on the recognition of a difference in the oxygen content between successive cardiac chambers, while this indicator-dilution method is based on the determination of the presence or absence of abnormally recirculating indicator. In any event, in actual practice, dilution curves sampled from the venae cavae and right atrium exhibit smooth contours and the detection and correct localization of both atrial and ventricular septal defects have been accomplished repeatedly. Application of the present method may, however, be limited in patients with severe congestive heart failure or valvular regurgitation on the right side of the heart. Although the dilution curves are undoubtedly modified by the relatively large and variable volume of blood contained within the cardiac catheter and its connection to the densitometer,[21] the detection and localization of a shunt are not based upon the configuration of a single curve, but rather on a comparison of curves obtained proximal and distal to the entry of the shunt.

In a small group of patients left-to-right shunts may be multiple or have unusual origins or terminations. In such patients, dye curves obtained from the right side of the heart after intravenous injection may be used in conjunction with curves recorded

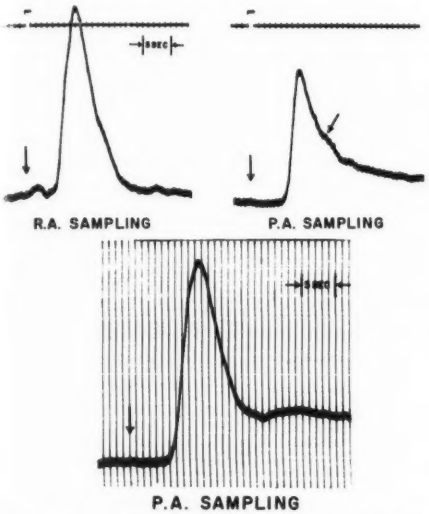

FIG. 5 *Top.* Dilution curves following peripheral vein injection in a patient with a very small ventricular septal defect whose nitrous oxide test showed a pulmonary-to-systemic flow ratio of 1.14.[17] *Oblique arrow* on the pulmonary artery curve (*right*) indicates the presence of recirculating dye. The normal right atrial curve (*left*) excludes the presence of an atrial septal defect.

FIG. 6 *Bottom.* Dilution curve obtained from the pulmonary artery after peripheral venous injection in a patient with aortic stenosis. The normal curve in this location excludes any left-to-right shunt. The presence of indicator, which has recirculated normally through the systemic circulation, interrupts the lower portion of the descending limb.

from a peripheral artery after left heart injection.[9] The former approach indicates the site of entry of a left-to-right shunt, while the latter demonstrates its site of origin. An alternate method[22, 23] is the injection of dye into the left side of the heart or aorta while sampling from the right side. The latter technic demonstrates both the origin and entry of the shunt.

SUMMARY

A simplified indicator-dilution technic for the localization of left-to-right shunts is described. Cardiogreen dye was injected into a peripheral vein and sampled from a catheter located in the vena cava, right heart, or pulmonary artery. When the site of sampling was distal to the entry of a shunt, the dilution curve was modified in a characteristic manner by the abnormally recirculating indicator. The chief advantage of this approach is that it obviates the necessity for left heart catheterization or the insertion of either 2 catheters or of a double-lumen catheter.

The accuracy of this dye-dilution method was proved in a group of dogs with experimentally produced left-to-right shunts, and its clinical applicablity was demonstrated in 16 patients with and 8 patients without shunts.

SUMMARIO IN INTERLINGUA

Es describite un simplificate technica a dilution de indicator pro le localisation de shuntings sinsitro-dextere. Le colorante cardio-verde es injicite in un vena peripheric e specimens es obtenite ab un catheter in le vena cave, le corde dextere, o le arteria pulmonar. Quando le sito del obtention de specimens esseva distal con respecto al entrata del shunt, le curva de dilution esseva modificate in un maniera characteristic per le recirculation anormal del indicator. Le plus importante avantage de iste methodo es que illo evita le necessitate de catheterismo sinistro-cardiac o le insertion de 2 catheteres o de 1 catheter a passage duple.

Le accuratia de iste methodo a dilution de colorante esseva demonstrate in un gruppo de canes con shunts sinistro-dextere de origine experimental. Su applicabilitate clinic esseva demonstrate in 16 patients con shunts e in 8 sin tales.

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Surgical Removal of an Intracavitary Left Ventricular Myxoma

By Jerome Harold Kay, M.D., Robert M. Anderson, M.D., John Meihaus, M.D., Reuben Lewis, M.D., Oscar Magidson, M.D., Sol Bernstein, M.D., and George C. Griffith, M.D.

PRIMARY intracardiac tumors of the heart are rare. The commonest primary tumor is myxoma, found almost exclusively in the atria, 75 or more occurring in the left atrium. Mahaim[1] reported 200 primary cardiac tumors in 1945, from the world literature up to that time. Strauss and Merliss[2] reviewed 480,331 autopsies from the Los Angeles County Hospital and were able to report 8 cases of myxoma occurring in the left atrium.

Myxoma originating in the ventricles appears to be extremely rare. A well-documented pathologic study of a left ventricular myxoma with embolic occlusion of the abdominal aorta and renal arteries was published by Young and Hunter[3] in 1957. The patient was a 10-year-old girl diagnosed as having rheumatic heart disease because of her cardiac disability and a rough mitral systolic murmur transmitted to the axilla and over the precordium. At autopsy a tumor was found practically filling the left ventricle and extending up to the aortic valve. The tumor was jelly-like, with multiple polypoid extensions. The tumor was attached to the endocardium below the insertion of the posterior papillary muscle of the mitral valve. We have found no report of a similar tumor in the recent literature.

The following is a case report of an intracavitary left ventricular myxomatous tumor, which was removed by the left transventricular route with the aid of cardiopulmonary bypass. This is apparently the first such tumor removed from the left ventricle.

Case Report

In October 1942, at the age of 15, the patient developed an embolus at the bifurcation of the aorta, and the following month the left leg was amputated below the knee. Thereafter, she had 3 children without incident. In April 1950, at the age of 23, she had a cerebral embolus with a left hemiplegia and shortly thereafter gave birth to her fourth child. The hemiplegia gradually improved until there was no residual disability. During this period of time there were multiple peripheral emboli despite long-term anticoagulant therapy with Dicumarol. From August 1955 to April 1959, 4 aortic emboli occurred that required surgical removal.* In 1956 a left thoracotomy was performed and at that time a multilobulated tumor was palpated in the left ventricular cavity. The mitral valve was normal to palpation.

The patient entered the St. Vincent's Hospital on February 10, 1959. There was a left ventricular thrust at the apex that had a peculiar double quality. There was also a palpable systolic click. A loud midsystolic sound was present that varied irregularly in intensity. No sounds or murmurs were heard in diastole. The second sound was normally split but not accentuated (fig. 1). The blood pressure in the left arm was 125/70. The right radial pulse was markedly diminished and both femoral pulsations were diminished. The lungs were clear, the liver was not enlarged, there was no edema, the venous pressure was not elevated, and no abnormal venous pulsations were detected.

The blood and urine examinations were normal. X-ray showed an unusual contour with prominence of the left ventricle and pulmonary artery. There was no evidence of enlargement of the left atrium. There was an adhesion to the pericardium, just above a segment along the left border, in the

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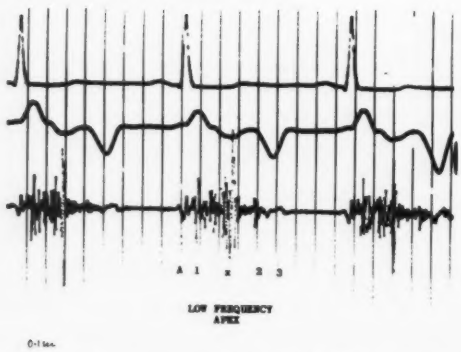

FIG. 1. Low-frequency phonocardiogram from the apex. *A*, atrial sound; *1*, first sound; *x*, loud mid-systolic sound; *2*, second heart sound; *3*, third heart sound.

region of the left ventricle, which had been noted on fluoroscopy to be noncontractile (fig. 2). An electrocardiogram revealed sinus rhythm at a rate of 75 per minute with evidence of left ventricular hypertrophy and digitalis effect (fig. 3).

Surgery was performed with the use of the Kay-Anderson heart-lung machine.[4] A median sternotomy incision was made. The pericardial sac was opened. The heart was adherent to the pericardial sac due to prior cardiac exploration. The adhesions were freed by blunt and sharp dissection. Tapes were placed around the superior and inferior venae cavae. The left ulnar artery was isolated immediately distal to its origin from the brachial artery. The left femoral artery was exposed immediately distal to Poupart's ligament. The patient was given 3 mg. of heparin per Kg. of body weight. A catheter was inserted in the left ulnar artery for measuring pressures. A second catheter was inserted into the left femoral artery to return blood to the patient. The catheters inserted into the left ulnar artery and the left femoral artery met obstructions, which were thought to be due to previous emboli. The right atrial appendage was opened. No abnormality was palpated in the right atrium or the tricuspid valve. A catheter was inserted into the inferior vena cava through the incision in the right atrium and also another catheter was passed into the superior vena cava through the right atrial appendage. The patient was placed on cardiopulmonary bypass, the aorta was cross clamped approximately 5 cm. above the origin of the coronary arteries, and the heart was stopped by anoxia. The left ventricle was then opened wide. A very large tumor, approximately 7 cm. in diameter, was found to occupy the entire cavity. This tumor had many

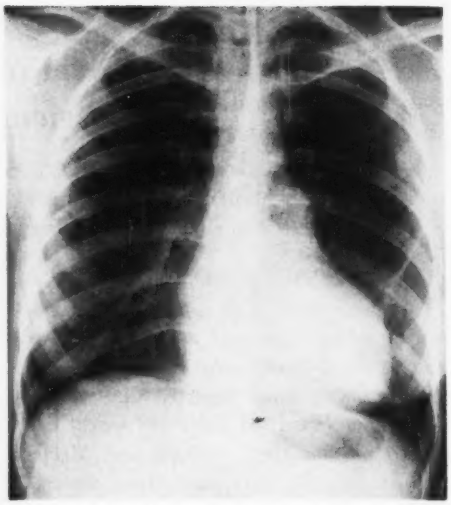

FIG. 2. X-ray showing unusual contour with prominence of left ventricle and pulmonary artery.

villous projections and apparently was arising from the lowermost portion of the ventricular septum as well as from the anterolateral portion of the wall of the left ventricle. Villous projections of the tumor protruded into the mitral valve as well as up into the aortic valve (fig. 4). The tumor was excised from its attachment to the septum and to the anterolateral wall of the left ventricle, a portion of the normal wall of the left ventricle being removed including 3 chordae tendineae in the midportion of the aortic leaflet of the mitral valve (fig. 5). To avoid incompetence of the valve, it was repaired with interrupted silk stitches (fig. 6). After the left ventricle was closed, ventricular fibrillation developed that was stopped with a countershock of 200 volts at 0.1 second. The cardiopulmonary bypass was removed after a total duration of 54 minutes. After 5 minutes the blood pressure fell to 30 or 40 mm. and a grade III or IV systolic thrill was felt in the left atrium. The cardiopulmonary bypass was begun and the left ventricular incision was reopened. The previously placed stitch in the aortic leaflet of the mitral valve was removed; this time the lateral third of the aortic leaflet of the mitral valve was sutured to the lateral third of the mural leaflet and this in turn to the lateral papillary muscle (fig. 6). This procedure narrowed the orifice of the mitral valve very slightly, if at all, but appeared to eliminate completely the mitral insufficiency. The left ventricle was again closed, the clamp was removed from the aorta, and the heart again developed ventricular fibrillation, which

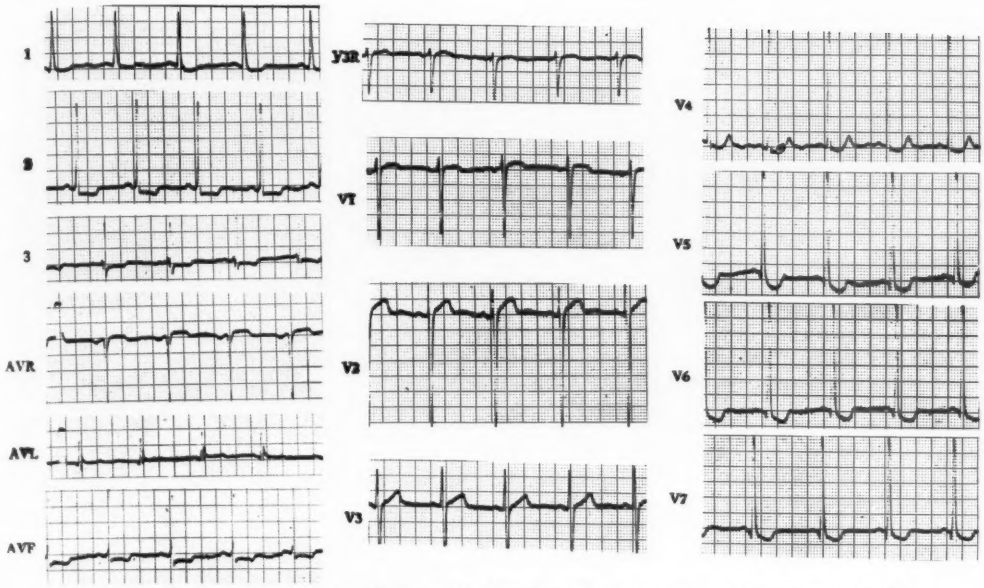

FIG. 3. Preoperative electrocardiogram showing sinus rhythm at rate of 75 per minute with evidence of left ventricular hypertrophy and digitalis effect.

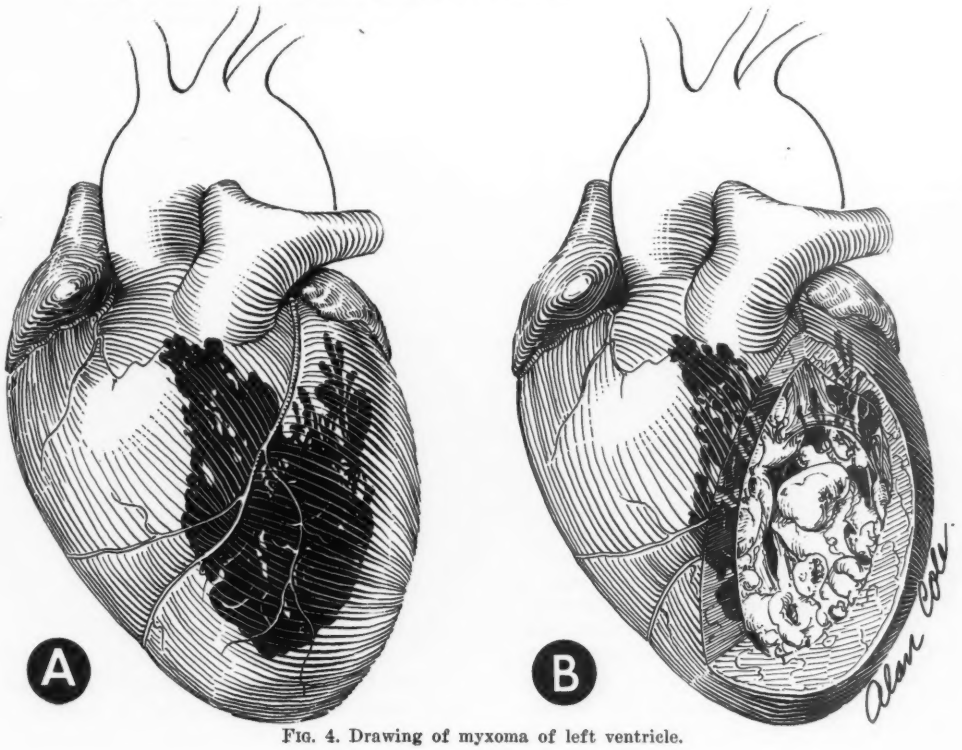

FIG. 4. Drawing of myxoma of left ventricle.

FIG. 5. Photograph of tumor.

was stopped again with one electric shock of 220 volts at 0.1 second. The cardiopulmonary bypass was disconnected again after a period of use of 29 minutes but after 5 to 8 minutes the heart began to beat poorly. Again the heart-lung machine was started to give the heart a period of rest, and this time was kept going for 38 minutes. Just before removal of the cardiopulmonary bypass 7 ml. of 1:10,000 epinephrine were injected into the right ventricular cavity. Despite previous digitalization, 0.8 mg. of lanatoside-C was also given. Again after 10 minutes the blood pressure began to fall. Three milliliters of 1:10,000 epinephrine were injected into the right ventricular cavity and the heart improved, whereupon the surgical closure was completed.

The tumor measured 7 by 6 by 3 cm., weighed 60 Gm. (figs. 7 and 8), and had a volume of 58 ml. Its peripheral portion was composed of smooth polypoid projections varying in size from 7 by 1 by 1 cm. to 1 by 0.3 by 0.3 cm. and in color from pale gray-tan to brown and to dark red. The periphery of the tumor was soft and jelly-like in consistency; near the base there was a stellate area of calcification. The base of attachment measured 3 by 2 by 0.4 cm.; here the soft tumor tissue was adherent to thickened white endocardium beneath which were 2 to 3 mm. of brown myocardium. Microscopically, the bulk of the tumor consisted of an amorphous nonfibrillary matrix, which stained pale pink with eosin, pale blue-green with Masson trichrome, blue-pink with phosphotungstic acid hematoxylin, very pale blue-pink with periodic acid fuchsin, and did not stain with Best's carmine. It varied in density from an

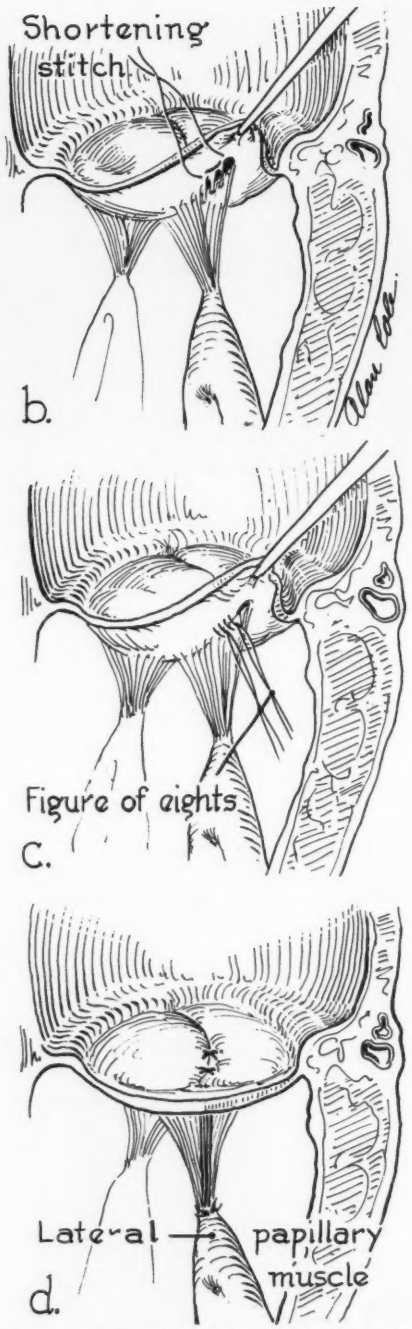

FIG. 6 *Top.* Drawing of first repair of aortic leaflet of mitral valve. *Middle and Bottom.* Drawing of final repair of aortic leaflet of mitral valve.

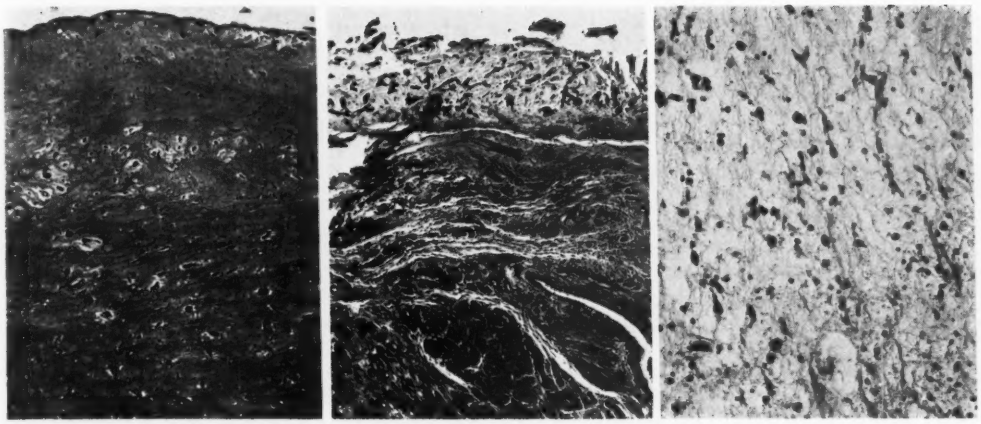

FIG. 7 *Left*. Photomicrograph of myxoma of left ventricle. × 400.

FIG. 8 *Middle*. Photomicrograph showing sharp transition between tumor tissue and underlying endocardium. × 100.

FIG. 9 *Right*. Photomicrograph of tumor embolus. × 400.

amost watery consistency to thicker material like Warthin's jelly or even colloid. It did not have the staining reactions of fibrin. There were few nucleated cells within the matrix; occasional minute fibrocytes with short fibrils extended in a stellate manner from the cell bodies, and clumps of endothelial cells formed small capillary spaces or solid buds. Throughout the tumor there were areas of recent and old hemorrhage. Near the base there was an area of fibrosis with calcification but no bone or cartilage cells were present. There was a sharp transition between the tumor tissue and the underlying endocardium, which was several times normal thickness, due to increase in both fibrous and elastic tissue. Neither fibrous or elastic fibrils entered the tumor from the endocardium.

The staining reactions exclude the possibility that the tumor matrix had its origin from either fibrin or fibrous tissue. The absence of a well-vascularized fibrous base between the endocardium and the tumor tissue further excluded the possibility that the lesion was an organized thrombus. The underlying myocardium contained no indication of infarction, old or recent. The diagnosis was made of myxoma of left ventricular endocardium (figs. 8 and 9).

Review of the sections from the tissue removed during previous embolectomies revealed the same tissue as was present inside the left ventricle. It was definitely myxomatous tissue rather than thrombus (fig. 9).

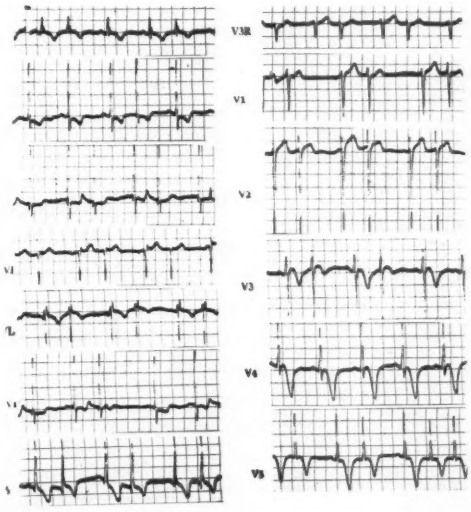

FIG. 10. Electrocardiogram 2 weeks after surgery.

On the second postoperative day a transient nodal rhythm appeared. An electrocardiogram taken 16 days postoperatively showed some ectopic nodal beats and deep symmetrically inverted T waves in leads V_3 through V_6, which were thought to be due to reaction around the incision of the left ventricle (fig. 10). An electrocardio-

gram taken 3 weeks later showed less marked T-wave changes.

Ten days after operation the apical impulse was less thrusting and without the previous double quality. The heart sounds were normal, the loud variable systolic click having disappeared. There was a grade II systolic murmur at the apex.

The patient was discharged from the hospital 21 days after the operation and she returned to Montana by car 1 week later.

Addendum

For 2 months after surgery the patient has been leading the normal life of a housewife.

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It is a common error to think that the more a doctor sees the greater his experience and the more he knows. No one ever drew a more skilful distinction than Cowper in his oft-quoted lines, which I am never tired of repeating in a medical audience:—

Knowledge and wisdom, far from being one,
Have oft-times no connexion. Knowledge dwells
In heads replete with thoughts of other men;
Wisdom in minds attentive to their own.
Knowledge is proud that he has learned so much;
Wisdom is humble that he knows no more.—William Osler, M.D.
The Student Life. Farewell Address to American and Canadian Medical Students. Med. News. (N.Y.), 1905

Use of Tape-Recorded Heart Sounds in Screening of Children for Heart Disease

By JACQUES M. SMITH, M.D., ROBERT A. MILLER, M.D., CARL MARIENFELD, M.D., BETTY HAHNEMAN, M.D., AND JOEL WILLARD, B.S.

An automated tape-recording unit for use in screening large populations of school children for heart disease has been developed and field tested. A technician can produce good quality apex and base heart sound recordings from 250 children during an average school day. The physician can listen to these recordings at a rate of 140 children per hour, recalling for examination each child considered to have an abnormal recording. Since almost all heart disease in children has some acoustic manifestation, a screening technic based on the heart sounds seems to be a logical one. The studies done with this unit have demonstrated its ability to select children with heart disease from a large number of normal children. Agreement between readers is satisfactory, and the number of "false positives" is considered reasonable.

THE recent dramatic progress in the diagnosis, treatment, and surgical correction of heart disease has stimulated renewed interest in the prevalence of cardiac problems in the school-age child. The practicing physician has become increasingly aware of congenital heart disease, so that at the present time these malformations are thought to consitute at least half and probably more than half of the total cases of heart disease in children.[1, 2]

Various cities in the United States maintain registries of heart disease in children, especially rheumatic heart disease; but in most instances these cases represent a relatively small proportion of the actual number of affected children.

There are over 25 published studies on the incidence of heart disease in school children (table 1), 5 of which have appeared since 1945.[3-19] These studies are based on clinical examination by workers with widely varied training and experience. The older studies tend to show a higher over-all incidence of heart disease and a marked predominance of rheumatic heart disease. More recent studies show lower incidence and a more even distribution of the cases between congenital and acquired heart disease. The scope of all these studies was limited to relatively small numbers of children by the laborious and time-consuming technic of physical examination as applied to large numbers of individuals.

On the basis of the published data one may make 2 assumptions: 1. There are probably 4 or more cases of heart disease in every 1,000 school children. 2. In many of these cases neither the parents nor the family physician of these children is aware that they have heart disease.

The nature of heart disease in children is such that it almost always alters the characteristics of the normal heart sounds or produces a murmur. The very high incidence of significant murmurs in heart disease of childhood is in direct contrast to the situation in adults, in whom a large proportion of coronary and hypertensive heart disease occurs. It would seem, therefore, that the most logical approach to cardiac case-finding in children would lie in the field of auscultation. Phonocardiography or other graphic methods of registering the heart sounds of children have been shown to be unsatisfactory as a screening device for heart disease.[20] The high incidence of innocent murmurs in childhood and the problem of extraneous noise

A project of the Children's Screening Committee of the Chicago Heart Association.

TABLE 1.—*Incidence of Heart Disease in School Children*[15]

	Total school population examined	Organic heart disease per cent
New York City, 1915	278,174	1.50
New York City, 1918	250,000	1.60
New York City, 1918 to 1922	1,336,343	1.39
New York City, 1921	44,000	0.50
Chicago, 1923	158,826	0.90
Philadelphia, 1924	23,671	0.63
Chicago, 1924	153,671	1.50
Chicago, 1925	130,260	1.70
Boston, 1927	119,337	0.52
Philadelphia, 1929	10,333	0.91
Florida, Illinois and Missouri, 1929	17,974	1.00
Cincinnati, 1927	6,960	0.37
Rochester, Minn., 1931	1,328	0.70
New York City, 1931	2,691	1.10

	Grade in school	Children	
New Haven, 1934			
"Better School"	1	1,144	1.32
	5	1,123	1.42
"Poorer School"	1	1,863	1.93
	5	1,628	2.08
Philadelphia, 1937			
Elementary		33,293	0.50
			0.30*
High School		9,154	0.90
			0.40*
San Francisco, 1938		13,338	0.37
Cincinnati, 1938		85,389	0.36
			0.12*
Louisville, 1941		41,905	0.52
Denver, 1945			1.09
Iowa, 1946		5,058	0.47
San Francisco, 1948		57,768	0.44

*Possible heart disease.

limit the value of these technics when used alone. Clinical auscultation, on the other hand, is extremely time-consuming. In addition, it has been shown that there is much variability in the detecting and interpreting of heart murmurs among various examiners.[20] The great advantage of auscultation, as Rushmer has pointed out, is that it apparently involves "those characteristics of auditory perception that allow a person to recognize a familiar voice even when distorted by a telephone." This subjective advantage over the phonocardiogram, plus the ability to screen out other noise, are the advantages of auscultation.[20] It seems, therefore, a technic that retains the advantages of auscultation but is efficient enough to allow a few trained observers to screen rapidly large numbers of patients under rather standard conditions would be an ideal case-finding technic.

The tape recording of the heart sounds[21] has several distinct advantages over physical examination is mass-screening programs: 1. It does not require the presence of the physician. The recordings may be made by a trained technician. 2. Large numbers of children can be recorded on a single roll of tape, which in turn can be played back at the listener's convenience in a quiet room. 3. The listener can turn the volume up or down and can go back to a case that he is not sure about. 4. A permanent record of these heart sounds is available, so that in questionable cases a phonocardiogram may be made from the tape giving the advantages of both subjective and objective evaluations.

Normal auscultatory findings in children differ greatly from those in adults.[24] Both heart sounds are louder and the incidence of functional murmurs is very high in children. Examiners not acquainted with "this characteristic ability to 'hear better' are in danger of over estimating the auscultatory findings."[24] At rest, a faint systolic murmur can be recorded by the phonocardiogram in all children.[24] With sufficiently sensitive pick-ups one can record a systolic murmur in all normal 20-year-old subjects.[21] Direct phonocardiography reveals a systolic murmur in or over the pulmonary artery in all cases.[21] Mannheimer has shown in a study of normal children that about half of these innocent murmurs are too faint to classify even by phonocardiography.[24] Most of the functional murmurs of reasonable loudness have the familiar musical, vibratory, twang-

i string quality described by Still at the b ginning of the century.[25] The rest of these f nctional murmurs are those of the ejection t pe, soft systolic murmurs usually best h rd in the second left interspace, well s parated from the heart sounds, and asso- ated with normal splitting of the second s nd.[24, 26] These innocent murmurs become familiar as old friends to experienced ex- iners of large numbers of normal children. he heart sounds and murmurs in congenital d acquired heart disease in almost every se differ remarkably from innocent mur- urs in quality, frequency, amplitude, and ming.[26–28] There is a small group of pa- ents in which auscultation alone is insuffi- ient to make a definite determination be- ween innocent and pathologic murmurs.[15, 19] Also, a few cases of congenital and acquired heart disease have practically no auscultatory manifestations.

The use of heart sounds as screening material for the detection of heart disease in children, therefore, will create a group of "false positives," which include innocent murmurs of unusual quality or loudness, those in which the differentiation between organic and innocent murmurs cannot be determined from the sound, and those cases in which for various reasons the heart sounds themselves seem unusual. Also, a group of "false negatives," including such things as an occasional case of coarctation of the aorta without a murmur, some cases of myocarditis or hypertension, might be missed by auscultation alone.

In the past few years it has become possible to reproduce heart sounds and murmurs as they are heard through the stethoscope.[29] With this in mind, a study was begun in 1954 to investigate the feasibility of using high-fidelity tape-recording equipment in screening for heart disease in children. To investigate the ability of the readers to recognize abnormal auscultatory phenomena from tape recordings, a group of 100 patients was recorded. Some had congenital or acquired heart disease, and others had normal hearts; but in every case cardiac catheterization, x-ray of the chest, and electrocardiogram were done. The cases with known heart disease all had organic murmurs. With 4 readers listening to the recorded heart sounds, no case of heart disease was missed, and every "normal" recording was recognized. Next, the heart sounds of 1,200 children were recorded at the Cook County Children's Hospital and in 5 Chicago elementary schools. These recordings were reviewed by 3 physicians: a pediatric cardiologist, an adult cardiologist, and an internist. The prime object of this study was to determine the degree of agreement among the readers. The results are shown in table 2. Any 2 readings of the 1,200 recordings provided 1,200 comparisons. Since there were 3 pairs of readings, reader A and B, reader A and C, and reader B and C, a total of 3,600 comparisons was available from which to determine reader agreement. Actually, only 3 272 were analyzed for agreement and are shown on table 2. As can be seen, even with equipment considered at the time inadequate and with readers with quite different kinds of training, the degree of agreement was about as good as that demonstrated by pairs of readers of miniature chest x-rays.[30] In an attempt to improve agreement among readers a teaching roll of heart sounds was developed. This preliminary study also pointed up the need for (1) modification of the equipment in order to speed up the

TABLE 2.—*Results of Pilot-Recording Study*

Test	Both readings in pair negative	One reading negative one positive	Both readings in pair positive	At least one reading positive (b+c)	Per cent agreement on positives $\frac{c}{d} \times 100$
	(a)	(b)	(c)	(d)	(e)
Heart sounds	2,923	264*	85*	349	24.3
Reading x-rays for tuberculosis	1,714	69	24	93	25.8

*Uncertain readings are included as positive.

FIG. 1. Automatic tape-recording unit used in screening project. See text for description.

recording rate, (2) simplification of the technical job of making the recordings so as to lessen technician fatigue, and (3) simplification of the administrative problems of mass-screening projects such as the identification of the patients and the maintenance of good records. This study also showed a need for improvement in the quality of the recorded sounds, specifically in the microphone, pointed up the problems of varying volume depending on the thickness of the chest wall, the size of the children, the need for reduction of room noise, and the difficulty of eliminating alternating current hum in the varying circumstances of recording in different locations.

METHODS AND MATERIAL

The recorder (figs. 1 and 2) was a Berlant BAX automatic, modified by replacing power supplies to use direct current from a battery pack for the "A" supply (*15A*), and an especially built highly filtered AC/DC power supply (*15B*) for the "B" source (*1B*). Additional modifications of the circuitry reduced noise and permitted operation of this recorder with associated equipment. The recording rate was 7½ inches of tape per second, and the frequency response of the unit was plus or minus 3 db. from 30 to 10,000 cycles.

A Berlant 4-channel mixer (*2*), modified by the installation of remotely operated relays in each of the input channels, was used to control volume and to mix the incoming signals which identified the position of the microphone on the chest, the audio-announced identification number of the patient, and the heart sound signal. The frequency response of this mixer matched that of the recorder.

An automatic volume control (*3*) maintained the signal level of the amplified heart sounds within a pre-set range without the necessity for the operator to adjust constantly the recording volume.

The microphone (*4*) was a crystal type with a frequency response of plus or minus 1 db. from 26 to 1,500 cycles per second.

The microphone was encased in an aluminum cup-shaped holder (*5*) connected to a vacuum

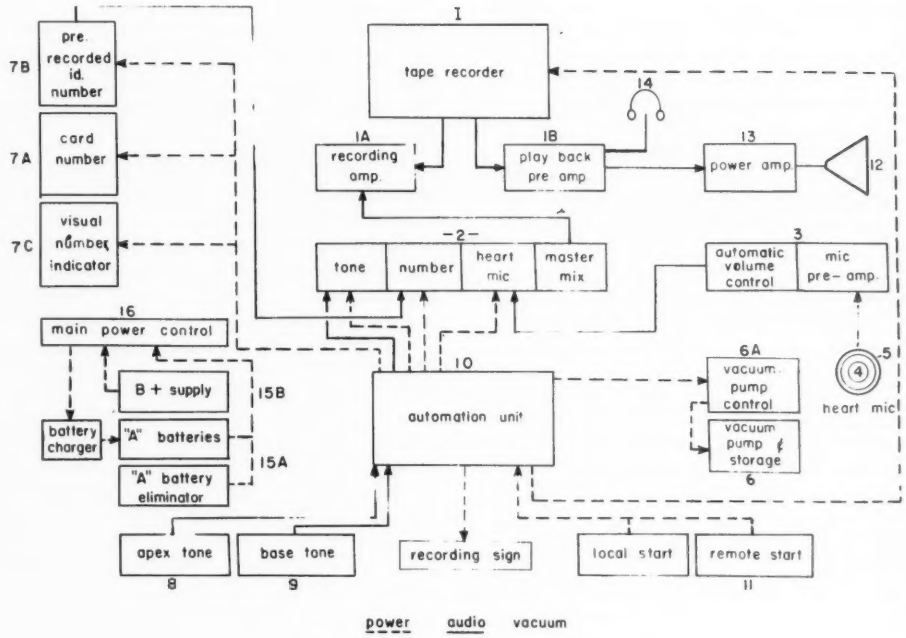

Fig. 2. Equipment block diagram.

storage tank (*6*). When the microphone and holder were placed against the chest, vacuum suction held the microphone in position at the predetermined pressure. It relieved the operator of the task of holding the microphone, eliminated the noise generated by the fingers of the operator and the movements of the skin of the subject, and served to block the majority of room noises. The microphone pressure control helped to eliminate the distortion caused by excessive pressure on the microphone diaphragm. The vacuum was released automatically, at the completion of a recording by a relay, a solenoid valve and a microswitch that locked into a specially built automation unit. A vacuum gage, power switch, and selector switch were provided so that the unit might be operated either manually or automatically.

The children being screened were identified in 2 ways. A Simplex electric numbering machine (*7A*) was used to stamp identifying numbers on the subjects' identification cards. It was modified to stack the cards automatically after they were stamped and to operate with a 16-mm. magnetic film (*7B*), a prerecorded series of consecutive identification numbers in the same sequence as those numbers stamped on the identification cards by the numbering machine. The listener, therefore, heard the patient identified by number and could be sure that that patient was correctly identified by a similarly numbered card.

A solenoid-operated Veeder-Root counter (*7C*) was interlocked with the numbering machine to provide the operator with a visual indication of the number of the case being recorded.

The listener was always aware of the position on the chest from which the recording was made by a one-half second, 1,000-cycle tone (*8*) recorded on the tape to indicate the apex recording. A similar 400-cycle tone (*9*) indicated the base of the heart. Two transistorized tone generators controlled by a microswitch in the automation unit provided the signals.

The automation unit (*10*), which was designed especially for the task, controlled the entire sequence of recording. The unit was activated by a foot switch (*11*). Ten microswitches activated by milled cams on a common shaft controlled the sequence of timing during the recording cycle. The technician placed the microphone in its vacuum holder over the apex of the heart, and stepped on the foot switch. The machine now automatically started the tape-drive mechanism on the tape recorder and activated the recording bias, turned off the vacuum pump motor, and opened the solenoid

valve to furnish a vacuum for the microphone holder. It then selected the musical tone that identified the apex microphone position and fed the signal to the tape, activated the card numbering machine, and stamped the cards automatically with the identification number, then activated the 16-mm. film play-back machine, which announced the same number on the tape. The microphone was now activated and recorded 11 seconds of heart sounds at the apex. The unit now automatically shut off the tape recorder and released the vacuum to the microphone holder. The technician saw that the microphone had been released from the chest and had only to pick it up and place it over the second left interspace, then stepped on the activating foot-switch again. The automation unit started the cycle again, this time, however, identifying the recording as coming from the base of the heart by the other musical tone. It then bypassed the subject-numbering machine, since this second recording was from the same person. The entire recording cycle, apex and base, was 25 seconds in length. The technician was supplied with monitoring speaker (*12*), a power amplifier (*13*) and a pair of Cambridge stethoscope-type earphones (*14*), so that he could check the quality of the recordings. The entire unit, with its battery power supplies (*15A* and *15B*) and control panel (*16*) was housed in 2 specially designed portable consoles, each of which divided in half for easier portability.

The recording team consisted of the recording technician and an administrative aid. Arrangements were made for additional help with the dressing and supervision of the children from the school nurse or other volunteers. Prior to the day of the recording, information was supplied to the parents, informing them of the screening procedure and requesting permission to make the recordings on their children. For each schoolroom a master sheet was prepared, which included the names of all the children and indication whether permission had been granted for recording. Each child was given his identification card and his presence was noted on the master sheet. As the individual was to be recorded, he handed his identification card to the administrative aid, who placed it in the Simplex stamping machine, which automatically numbered his card during the recording procedure. The child undressed to the waist and lay down. The technician then placed the microphone over the apex of the heart and activated the automation unit. With the recording sequence it was possible to record 2 children per minute. However, 60 children per hour was a more reasonable rate and this should be modified to account for delays in bringing children to the equipment. Taking into account the necessary adjustments to meet school schedules, we have found that over an extended period of time a recording rate of about 250 to 300 children per school day was quite practical.

Play-Back Procedure

It has been found that a training period is necessary for the listener to become proficient. The training was provided by means of a training reel that allowed the listener to become familiar with the identifying tones of the microphone position, the quality of the heart sounds, murmurs, breath sounds, and the identification voice. In addition, it allowed him to listen to normal and abnormal heart sounds and murmurs in rapid sequence and to familiarize himself with the characteristics of these sounds as heard through a speaker or earphones. This training reel was made up of recordings selected from a group of 100 proved cases of congenital and acquired heart disease and from a group of normal children.

Following this period of training, the listener found that a recording of 11 seconds at the apex of the heart and 11 seconds at the base was of adequate length for screening purposes without causing undue fatigue. The normal screening rate for a trained listener was 140 patients per hour. For maximum efficiency, we have found that listening sessions should not exceed 1 hour. As he listened to the tape, the physician used an electric adding machine to record his results. The subjects identification number was indicated in the hundreds and thousands column. The presence or absence of murmurs or the inability of the reader to interpret the heart sounds because of technical difficulties was recorded in the tens column. The disposition of the case, that is, recall for examination, no recall, or inability to decide because of technical difficulties was recorded in the units column.

Findings (in tens column)
- 0—no murmur
- 5—technically unsatisfactory
- 9—a murmur present

Disposition (in units column)
- 0—no recall
- 5—no decision because of technical difficulties
- 9—recall

In addition to the "9," the subtract button was used to put a dash behind a recall indication. This helped to prevent errors by requiring the reader to perform 2 different and distinct acts in indicating a recall and also simplified the finding of recalls in a long column of figures.

Examples

279 00 (case 279, no murmur, no recall)
280 90 (case 280, murmur, no recall—reader considers murmur innocent)
281 99 (case 281, murmur, recall)
282 55 (case 282, recording technically unsatisfactory, no decision could be made)

It should be stressed that the physician listening to the tape was not trying to make a diagnosis. He was attempting, from a rapid sequence, to pick out those patients that should be recalled for examination.

Field Studies

A number of studies have been conducted for the purpose of testing the components of this equipment and the administrative efficiency of the operating procedure.

Field Study No. 1. At a local private institution, 99 children were examined (auscultation only) by each of 3 members of the screening team. Heart sounds of these same children were recorded in an area separate from the examining room. The recordings were studied twice by each of the 3 physicians, once using Cambridge stethoscope-type earphones for the play-back of the tape, and once using a speaker in a quiet room. The physicians worked independently and their findings were not revealed to each other during the studies.

Approximately 30 days after this recording session, each of the children was re-examined This time, however, the 3 examiners acted as a consulting team examining the children together. In addition, they had the results of 70-mm. chest x-ray and the medical history of the child. On the basis of this examination, the physicians arrived at a "conference finding" for each child. These conference findings classified the children as having normal or abnormal heart sounds and constituted the standard against which the type recordings could be compared (table 3). The number of false positives was relatively small, and no case of actual heart disease was missed by the screening technic. The efficiency of the screening physician using tape recordings was equal to that from his auscultation.

TABLE 3.—*Conference Findings in Ninety-nine Cases*

Reader	Live	Tape via speaker	Tape via phones
Cases recalled			
A	4	6	5
B	6	4	4
C	6	5	6

4 Definite heart disease, 2 cases requiring further observation, 93 no heart disease.

Field Study No. 2. In this study, a recording technician taped the heart sounds of 507 children from a local foundling home.

These tapes were listened to by 4 of us and, on the basis of the play-backs, 16 of the children were recalled. These were subsequently examined by 3 of us, and 1 child was found to have definite heart disease. Two other children had murmurs which we thought were probably not significant but would require additional laboratory and clinical observation.

It was not until after these studies were completed that the participating physicians were informed that this particular school carefully excludes children with heart disease. The one child, found by the screening technic to have significant heart disease, was a known case in which the school had made an exception. There are 2 observations that may be made from this study. The rate of false positives (15 out of 507 children) 2.6 per cent seems to be a reasonable figure. Although there was only 1 case of heart disease in the entire group, or an incidence of approximately 0.2 per cent, the case was not missed by the screening technic.

Field Study No. 3. The heart sounds of 1,020 children were recorded in a local elementary school. The tapes were read by 3 physicians and the results of these readings are shown in table 4. The children recalled by the screening program were subsequently examined by the same 3 physicians.

The significant findings in this project were that out of 1,020 children 40, or 4.0 per cent, were recalled. Of these children, 7 were found to have definite heart disease.

TABLE 4.—*Results of Tape Recordings Field Study No. 3*

Total recorded on tape	1,020
Total recalled	40
Referred for follow-up care	10
1. Definite heart disease	7
2. Probably normal, but need further observation	3

Three other children warranted further follow-up because a decision could not be made from the murmur alone.

Therefore, 17.5 per cent of the recalls were found to have definite heart disease, and a total of 25 per cent of the recalls warranted follow-up study by their physicians. Another important fact is that of the 7 children found to have heart disease, there was knowledge of this in only 2. Neither the parents nor the family physician knew of the existing heart disease in the other 5, even though a periodic physical examination is required of all students in the public schools. Furthermore, this incidence of 7 cases of heart disease per 1,000 is in agreement with published surveys. These figures vary from about 4 to 15 per 1,000 in the school age group.

DISCUSSION

Aside from any other uses of this tape-recording technic, its value in a case-finding program should be clear. In an era when every child with rheumatic heart disease should be on prophylactic antibiotics and every child with congenital heart disease is considered a potential surgical candidate, a practical case finding method is needed. The reports of Robinson,[19] who found 4.4 cases of heart disease per 1,000 in the San Francisco schools, Rauh,[15] who found 5 cases per 1,000 in the Cincinnati schools, Weiss,[16] 5 per 1,000 in Louisville, and Jackson,[18] 5 per 1,000 in a rural Iowa county are only a few of the mass of data testifying to the large numbers of children with heart disease in our school system. There are probably 2,500 to 5,000 schoole-age children with heart disease in Chicago alone. It is not feasible to have a trained cardiologist examine hundreds of thousands of normal children in order to screen for cases of heart disease. We can, however, bring the children to the cardiologist via the technic of high-fidelity tape-recorded heart sounds. With the installation of this recording equipment in a sound-proof trailer, it would seem quite practical to survey large populations of school children for heart disease, in a way quite comparable to the mass x-ray surveys for tuberculosis.

We are quite aware of the potential psychological problems that might be created by recalling a normal child for cardiac evaluation. It should be possible to keep this at a reasonable minimum with proper educational material for the parents, the teachers, and the children. The relatively low recall rate of false positives, approximately 30 cases per 1,000, will also tend to obviate this problem. More important, however, has been the gratifying experience of the screening physician in being able to free the normal child sentenced to limited activity because of erroneous diagnosis of heart disease.

The opportunity to "set straight" those children restricted because of loud functional murmurs previously considered organic, is an aspect of case-finding often overlooked.

SUMMARY

In an analysis for agreement of 3,272 comparisons between listeners of tape-recorded heart sounds, the degree of agreement was about as good as that demonstrated by pairs of readers in miniature chest x-rays. This pilot study was accomplished with equipment considered inadequate and with listeners of widely varied training.

A specially built, automated tape-recording unit has now been developed which makes screening for heart disease in large numbers of individuals practicable.

A technician can record approximately 250 children a day in the average Chicago public school. After a brief training period, the physician-listener can screen 140 children in an hour, recalling those who require a

physical examination. Field studies with this equipment have shown that the number of normal children recalled is low and that practically no heart disease with abnormal heart sounds and murmurs is missed. It is thought that this technic offers a practical way to screen large populations of children for heart disease.

Acknowledgment

The authors wish to express their appreciation for the valuable assistance and continuing interest of Mr. Louis deBoer, Executive Director of the Chicago Heart Association, who gave the original impetus to this project. We also wish to thank Dr. Arthur E. Rikli, Dr. John McDonough, Mr. Philip Enterline, and Miss Gloria Labbe of the Heart Disease Control Section, U. S. Public Health Service, for their advice and statistical help. Dr. Edward Press and Dr. Simon Rodbard also aided us in the early stages of this project.

Summario in Interlingua

In un analyse del correlation de judicamento inter pares de auditores de 3.272 phonomagnetogrammas de sonos cardiac, le grado de accordo esseva simile a illo demonstrate per pares de interpretas de microroentgenogrammas thoracic. Le hic-presentate studio, de character preliminari, esseva executate con equipamento considerate como inadequate e con auditores de differentissime experientia.

Un automatic apparato phonomagnetographic, specialmente construite pro le registration de sonos cardiac, es nunc disponibile, permittente le execution de tests discriminatori pro morbo cardiac in grande numeros de subjectos.

Un sol technico, usante le nove apparato, es capace a obtener phonomagnetogrammas cardiac ab approximativemente 250 juveniles per die sub le conditiones de labor que es typicamente incontrate in le scholas public de Chicago. Post un curte periodo de trainamento, le medico-auditor pote examinar le registrationes de 140 juveniles in le curso de un hora, reclamante le subjectos pro qui un examine physic es indicate. Studios comparative, con le uso del nove apparatura sub le conditiones del practica quotidian, ha demonstrate que le numero del subjectos normal reclamate es basse e que practicamente nulle caso de morbo cardiac con anormalitate del sonos cardiac e con murumures cardiac escappa al detection. Es opinate que iste technica representa un medio practic pro effectuar tests de discrimination pro morbo cardiac in grande populationes juvenil.

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CLINICAL EXPERIENCE

Others' follies teach us not,
Nor much their wisdom teaches;
And most, of sterling worth, is what
Our own experience preaches.

—Tennyson: *Will Waterproof's Lyrical Monologue.*

From C. Sidney Burwell, M.D., and James Metcalfe, M.D. *Heart Disease and Pregnancy. Physiology and Management.* Boston, Little, Brown and Company, 1958, p. 44.

Postural Effects on the Baselines of Ventricular Performance

By ROBERT F. RUSHMER, M.D.

In both dogs and human subjects, fully relaxed in the horizontal position, the ventricular dimensions and stroke volume are generally at or near maximal levels. During exertion the stroke volume does not progressively increase, indeed it rarely exceeds recumbent control values. On sitting or standing the ventricular size and stroke volume diminish to a new lower control level. When control values are measured during quiet standing, exertion produces a slight but consistent increase in stroke volume approximately to the level found in recumbency. This difference in the baseline for control values must be considered in evaluating the cardiovascular response to exercise.

MOST cardiovascular investigation is conducted on animals and human beings relaxed in recumbent positions to provide stable baseline conditions with long columns of blood oriented horizontally and the stresses on the cardiovascular system presumably at a low, constant level. Changes in performance of the ventricular chambers have been studied in intact dogs while they were running down a hall or on a motor-driven treadmill at 3 m.p.h. on a 5 per cent grade. During the first few series of experiments, a stable control baseline was achieved by allowing the dogs to remain reclining until just before the exercise began. Under these conditions the left ventricular dimensions were observed to diminish during the exertion. Subsequently, continuous recordings of left ventricular diameter, circumference, and length have all demonstrated that if the dogs are standing at the onset of exercise, the ventricular diastolic dimensions may diminish slightly, increase slightly, or most commonly, remain unchanged. The systolic deflections were usually slightly increased by more complete systolic ejection.

A survey of recent data on human subjects revealed that an increase in stroke volume was neither an essential nor a consistent feature of the cardiac response to exertion.[1] This conclusion was in conflict with the observation by Mitchell, Sproule, and Chapman[2] that stroke volume consistently increases about 2-fold from erect control values to maximal exertion. We are indebted to Chapman for his suggestion that this apparent discrepancy might reflect differences in control values, measured in the recumbent position in some studies and in the erect position in others.

Thus, conflicting conclusions have resulted from failure to recognize the nature of the change in baselines of cardiac performance that occur during a change from erect to recumbent position. In other words, it is important to appreciate the differences between the baselines of cardiac performance in erect and reclining human subjects and dogs.

METHODS

In the experiments on intact unanesthetized dogs, left ventricular performance was continuously analyzed in terms of several parameters during spontaneous activity. The technics employed for these studies have been described elsewhere[3–5] and are only summarized briefly here. Changing left ventricular dimensions were recorded continuously by means of gages applied directly to the ventricle during aseptic surgery. A modified sonar technic was employed to record left ventricular diameter.[4] Wires were led through the back, so that recordings could be made at will after recovery from the operation.

Effective left ventricular pressure was recorded through an indwelling cannula extending from the

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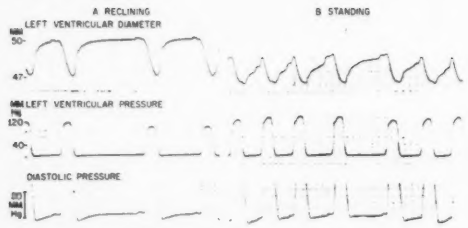

FIG. 1. *A*. Changes in left ventricular diameter and effective pressure during a succession of cardiac cycles in a relaxed recumbent dog. *B*. During quiet standing with the trunk horizontal, the heart rate accelerated, systolic dimensions and systolic excursion diminished and ventricular filling continued throughout diastole.

left atrium through the posterior thoracic wall. A polythene catheter (about 13 cm. long) from a miniature differential transformer pressure transducer was threaded through this cannula into the left ventricular cavity. From a balloon near the heart, intrapleural pressure was impressed upon the back of the gage, which then responded to effective ventricular pressure. Left ventricular pressure, amplified 4 times, was recorded to demonstrate changes in diastolic pressure.

Heart rate was indicated by a ratemeter triggered by the rapid rise of the ventricular pressure. During each cycle the galvanometer deflection indicated the reciprocal of the cycle length of the preceding cardiac cycle.

RESULTS

In dogs relaxed in the prone position, the heart rate tended to be slow (70 to 100 per minute) and sinus arrhythmia was frequently apparent (fig. 1*A*). The left ventricular diameter increased very rapidly during early diastole and reached a plateau. However, the diameter often continued to increase very gradually, even when the diastolic interval was very long. Atrial contraction contributed very little to ventricular filling under these conditions because the dimensions approached maximal distention during the rapid filling phase. When the dog stood quietly with his trunk oriented horizontally, the diastolic and systolic dimensions were both promptly reduced and the amplitude of the systolic defection was decidedly diminished (fig. 1*B*). The reduction in diastolic distention was accompanied by a reduction in diastolic filling pressure of no more than 2 mm. Hg. The hydrostatic column from the ventricle to the gage was exactly the same in the 2 records. In many instances no change in effective filling pressure was demonstrable.

The longest cardiac cycle in the standing record was longer than the shortest cycle in the reclining record, so the difference in diastolic and systolic dimensions in the 2 positions was not due solely to filling time. The ventricle filled much more rapidly in the standing position than in the reclining position. True diastasis was rarely noted in the standing position except during the compensatory pause following premature contractions. The relative degree of distention during early diastole was much smaller in the standing position. All these factors suggested that the distensibility of the ventricle was significantly different in the standing and reclining dog even though the trunk was horizontally oriented in both cases.

During the transition from the standing (or sitting) position to the reclining position, the diastolic and systolic diameter increased progressively with each beat until a plateau was attained after 5 or 6 cycles. As the end-diastolic diameter became larger and larger, the amplitude of the systolic excursion increased correspondingly.[5] This observation suggested that stroke volume and stroke work increased with greater diastolic distention, as would be predicted by Starling's law of the heart. Such a relationship between diastolic distention and systolic excursions was consistently observed during the transition from sitting or standing to the recumbent position.[5]

Reduction in diastolic and systolic left ventricular dimensions was produced consistently by passive tilting of 5 dogs by gently elevating the head end of a tilt board to approximately 30 degrees. Even when the animals did not stir, the left ventricular dimensions promptly diminished to a lower level, which was well maintained until the animal was returned to the horizontal position (fig. 2*A*). Tilting the dog with the head

own 30 degrees, produced a similar response though this could easily be obscured if the imal was not fully relaxed during the control period (fig. 2*B*). The orientation of the dy itself was not necessarily the prime factor in this reaction. If the dog was relaxed in ie prone position and merely lifted his head response to noise or movement elsewhere the room, the ventricular dimensions usually diminished promptly.

Passive tilting of human subjects is known o produce a diminution in cardiac output and n stroke volume. As an example, a reduction n stroke volume associated with an increase n heart rate after tilting normal subjects head up to 60 degrees was replotted from the study of Weissler et al. (fig. 2*C*). The reduction in stroke volume was probably greater during a passive tilt than during quiet standing because of the contraction of the weight-bearing muscles.

The difference between recumbent and standing baselines assumed importance in evaluating the left ventricular response to exertion (fig. 3). If a recumbent dog stood up just before he began to exercise on a motor-driven treadmill (fig. 3*B*), the left ventricular diameter abruptly diminished and effective filling pressure diminished at the same time. Under these conditions, the left ventricular response to exertion involved marked reduction in diastolic and systolic diameter along with an obvious reduction in systolic deflection with each cycle. The heart rate increased from about 90 to about 200 per minute. A few minutes later, the exercise was repeated, but this time the dog was standing during the control period (fig. 3*D*). The diastolic diameter was essentially unchanged and the stroke deflection was slightly increased by greater systolic ejection during exertion.

Although the increase in stroke was slight and the acceleration of the heart rate was great during exercise, the ventricular response must not be visualized as merely an increase in heart rate. The importance of this injunction was clearly demonstrated by artificial induction of tachycardia in the same animal while it was reclining quietly on a table. A pair of electrodes had previously been sutured to the atrial wall with wires leading to the outside. The changes in heart rate during a previous exercise response had been recorded and stored with a magnetic tape recorder.[5] When this tape was replayed through a stimulator connected to the pacemaker electrodes on the atrium, the changes in heart rate that had occurred during a previous exercise could be reproduced precisely (fig. 3*E*). Under these conditions, the diastolic diameter was profoundly reduced and the stroke deflections were also greatly reduced. Incidentally, the ventricular systolic pressure was also diminished in contrast with the elevation in pressure generally observed during exercise. Thus, although the increased cardiac output during exertion is dependent primarily on an acceleration of the heart rate, this adjustment apparently must be accompanied by adaptations in the peripheral circulatory beds and in functional characteristics of the myocardium, i.e., contractility.

In previous publications,[1, 6] evidence from 7 different series of experiments was presented to support the conclusion that an increase in stroke volume was not an essential feature of the ventricular response to exercise in normal human subjects. In some of these experiments, the subjects performed leg exercises while reclining on a fluoroscopic table,[7, 10] some performed exercises while seated on a bicycle ergometer,[11] and others walked or ran on motor-driven treadmills.[12, 13] The potential importance of posture not having been recognized in these responses, individual values for stroke volume, heart rate, and arteriovenous oxygen difference were plotted against oxygen consumption without regard for the posture of the subject during control and exercise determinations. In retrospect, this practice appears to be unwise in view of the importance of posture in the experiments on dogs illustrated in figure 3.

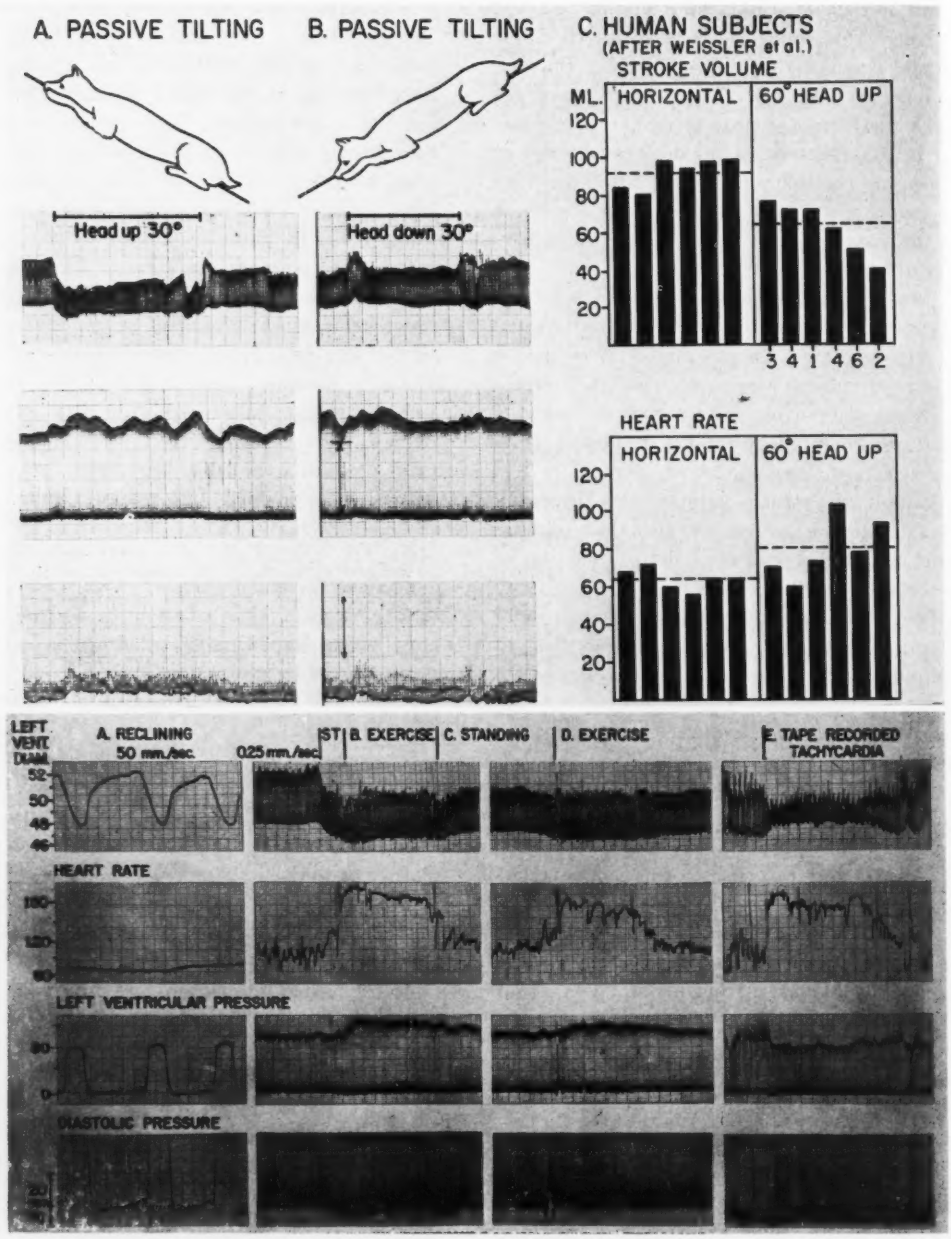

FIG. 2 *Top. A.* Reduction in diastolic and systolic diameter and stroke deflection on passive tilting of relaxed conscious dogs with the head up 30 degrees. *Top,* left ventricular diameter; *middle,* left ventricular pressure; *bottom,* diastolic pressure. *B.* Passive tilting with the head down 30° also produced a reduction in ventricular dimensions and systolic excursions. However, in this case the animal was not well relaxed during the control period but was relaxed

(Continued on bottom of next page)

To examine the influence of position on the changes in stroke volume, mean values from studies on recumbent and erect human subjects were plotted separately in figure 4*A*. Since oxygen consumption was recorded as milliliters per minute in some studies and as milliliters per minute per square meter in others, 2 scales are indicated on the abscissa. The studies by Donald et al.[7] and Barratt-Boyes and Wood[8] revealed no evidence of a progressive increase in mean values for stroke volume during exercise by recumbent subjects. On the other hand, Dexter et al.[9] reported data indicating a slight increase in stroke volume under similar conditions. The same kind of results were found among the subjects studied by Williams[10] and by Freedman et al.[15] (fig. 5*A*). On the other hand, 4 of the 5 series of experiments[2, 11-14] on erect subjects demonstrated average values for stroke volume that were lower during the control period than during exertion. The single exception was the experiment of Asmussen and Nielsen,[11] in which the control values were measured in the recumbent position and were not obviously different from values during levels of exertion increasing oxygen consumption as much as 10-fold. These data are consistent with the view that stroke volume remains essentially unchanged over a very wide range of physical exertion. Even at peak levels of exercise, the stroke volume did not consistently exceed recumbent control values.

The evidence that stroke volume did not increase progressively as the intensity of exertion was increased appeared inconsistent with the data reported by Mitchell, Sproule, and Chapman,[2] who found that stroke volume exceeded control values by about 2-fold

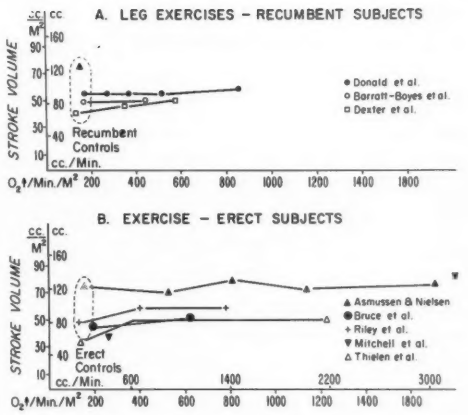

FIG. 4. *A*. Stroke volume in recumbent subjects during exertion sufficient to increase oxygen consumption several fold. *Dotted oval* encloses the recumbent control values. *B*. Erect control values for stroke volume tended to be slightly lower than in recumbent subjects. A progressive increase in stroke volume was not apparently associated with increased oxygen consumption due to exercise.

during intense exercise that produced a maximum oxygen consumption. In this study, Mitchell et al. measured oxygen consumption during progressively increasing work loads lasting 2½ minutes on a motor-driven treadmill running at 6 m.p.h. with the grade being elevated in increments of 2.5 per cent until oxygen uptake per minute leveled off. In some subjects, it was necessary to increase the speed as well as the grade and the maximum work load was 9 m.p.h. at 14.75 per cent grade. At a later date, both maximal oxygen consumption and cardiac output (by an indicator-dilution technic) were measured at rest and at 3 work loads. These data had not been included in the previous reports[1, 6] because it seemed inappropriate to plot heart rate or stroke volume against values of oxy-

following return to the horizontal position. *C*. In normal human subjects passively tilted 60° head up, stroke volume decreased and mean cardiac output diminished from 5.9 to 5.0 L. per minute in spite of accelerated heart rate (after Weissler et al.[16]),

FIG. 3 *Bottom*. *A*. Left ventricular diameter approached maximal dimensions in a recumbent dog. *B*. The diastolic and systolic dimensions diminished promptly on standing and during exercise on a treadmill at 3 m.p.h. on a 5 per cent grade. *D*. Little change in ventricular diameter during exercise following a standing control period (*C*). *E*. Artificially induced tachycardia caused a pronounced diminution of diastolic diameter and reduced systolic excursion.

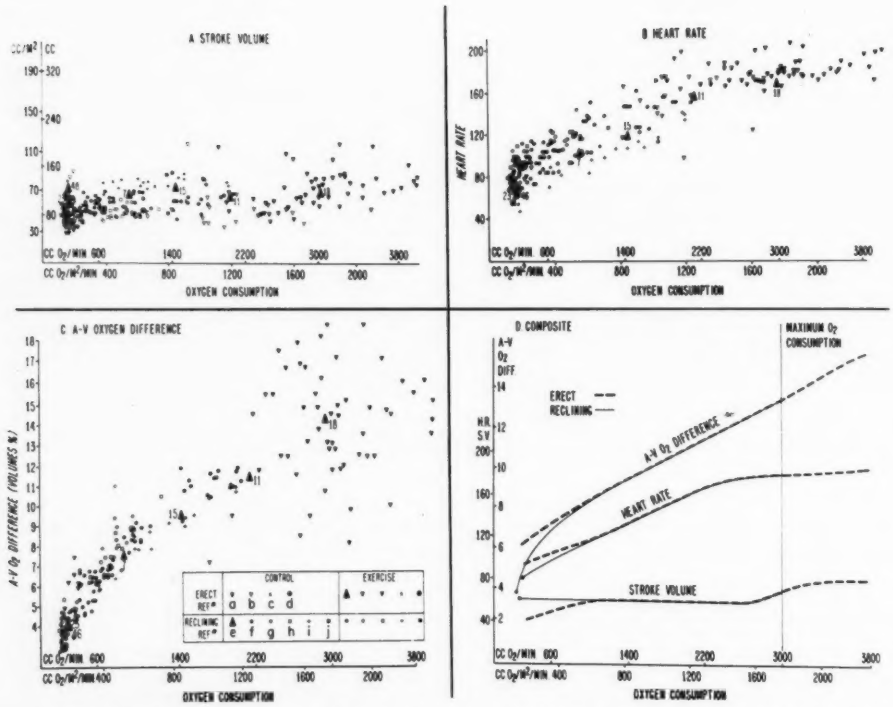

FIG. 5. The contribution of (*A*) stroke volume, (*B*) heart rate, and (*C*) arteriovenous oxygen difference to the delivery of oxygen during exertion. *Dotted lines*, erect subjects; *Continuous lines*, recumbent subjects. In the key, the symbols represent the following references: *a*, 2; *b*, 12; *c*, 14; *d*, 13; *e*, 11; *f*, 7; *g*, 8; *h*, 9; *i*, 15; *j*, 10.

gen consumption that had been pushed to a plateau (i.e., oxygen debt was accumulating rapidly). The mean control value for stroke volume of subjects standing on the treadmill were lower than most control values and considerably below the recumbent control values reported by Asmussen and Nielsen.[11]

The 3 factors that contribute to increased oxygen delivery to the tissues during exercise include stroke volume, heart rate, and oxygen extraction from the blood (arteriovenous oxygen difference). The relative contributions of these 3 factors are illustrated in figure 5, in which data from 10 different series of experiments have been compiled and identified with reference to the posture of the subjects during control measurements and exercise. In addition to the data previously reported,[1] this graph includes individual points from the study by Mitchell et al.,[2] plus previously unreported data from subsequent studies. Data from the studies by Riley et al.[14] and Freedman et al.[15] have also been included.

The stroke volume was surprisingly uniform over the wide range of exertion and oxygen consumption. In general, the values from erect subjects were lower at rest and slightly higher at maximal levels of exertion. The heart rate increased progressively to levels between 160 and 200 beats per minute and leveled off. The arteriovenous oxygen difference apparently increased progressively over the full range of oxygen consumption.

Our interpretation of the contribution of stroke volume, heart rate, and arteriovenous oxygen difference to the total oxygen delivery during physical exertion are indicated by

lines, drawn by eye, through the points on each graph and superimposed on a single chart (fig. 5*D*). Among most subjects studied while recumbent, stroke volume changed very little, as indicated by the light continuous line. In general, control values for erect subjects, indicated by the interrupted lines, revealed a faster heart rate and smaller stroke volume than those of recumbent subjects. Stroke volume of subjects exercising in the erect position did not increase above values typically observed in recumbent subjects until maximal oxygen consumption was attained (*interrupted lines*). Thus, stroke volume during exercise may increase in erect subjects primarily because their control values were lower than those of recumbent subjects. There does not appear to be a progressive increase in stroke volume associated with greater oxygen delivery or levels of physical exertion.

Discussion

Inattentive, recumbent dogs have heart rates generally ranging between 70 and 100 beats per minute and under these conditions, the left ventricle tends to function at or near its maximal dimensions as recorded by diameter, length, and circumference gages. In such circumstances, intravenous infusions of blood sufficient to elevate effective filling pressure by as much as 15 mm. Hg failed to increase left ventricular diameter by as much as 1 mm.[5] Any change in the status of the animal, including the administration of anesthetics, causes a reduction in the ventricular dimensions. Thoracotomy tends to reduce further the size of the cardiac chambers.[16] Thus, the exposed heart of an anesthetized dog functions at a baseline different from that for the recumbent intact animal. When an intact healthy dog stands up, his ventricular size diminishes, but this decrease does not necessarily imply that the new baseline corresponds to that for the anesthetized thoracotomized animal. Thus, at least 3 different baselines may require consideration in evaluating the physiology of cardiac function.

The change in size of the heart found in dogs has a direct counterpart in human subjects. For example, Sjöstrand[17] reported roentgenographic studies demonstrating that size of the cardiac silhouette was maximal in the recumbent position. Any change in the status of the individual induced either a reduction in heart size or no change. He was unable to cause the heart to expand beyond those dimensions. The fact that stroke volume and cardiac output diminish as a result of passive tilting with the head up,[18, 19] indicates that a reduction in stroke volume of smaller magnitude apparently occurs when average normal subjects stand up (figs. 3 and 4). During control determinations in erect subjects, the heart rate tended to be somewhat higher and the stroke volume appeared to be lower. In addition, anticipation of violent exercise may also be accompanied by a further cardioacceleration. The effect of this acceleration may correspond to the reduction in systolic deflections produced by experimentally induced tachycardia in dogs (fig. 3*E*). However, this is not the whole story because Barger et al.[20] reported that changes in cardiac output produced in resting dogs by excitement were frequently as large as those induced by moderate exercise. Anxiety and anticipation of exercise are generally recognized as causes of inappropriate tachycardia with a corresponding diminution in stroke volume if cardiac output is not significantly increased. In spite of the increased variability which was found during standing, this is probably the only reasonable baseline condition for control determinations if the exercise is to be performed in the same position. The parallelism between dogs and human subjects is somewhat surprising since the trunk is horizontal in the standing dog.

Summary

The ventricular chambers are frequently distended maximally while dogs and normal human subjects are relaxed and recumbent. Stroke volume also approaches maximal values under these conditions.

On sitting or standing, the heart diminishes and the ventricular stroke volume is reduced correspondingly in accordance with Starling's law of the heart.

The stroke volume increases but little during exertion and rarely exceeds recumbent control values. This increased stroke volume is generally achieved by increased systolic ejection, with little or no contribution by increased diastolic distention.

A distinction must be made between 3 baseline conditions during which control values are obtained in cardiovascular research: standing, recumbency, and after thoracotomy under anesthesia.

To evaluate cardiovascular effects of exertion while erect, it seems appropriate to obtain control values while standing quietly. Under these conditions, stroke volume is lower during the control than during exertion in most cases but not without exception. However, a progressive increase in stroke volume does not occur as the intensity of the exertion is increased.

ACKNOWLEDGMENT

I wish to express my gratitude to Dr. Carleton Chapman for his advice and suggestions as well as his kindness in providing individual values and previously unpublished data for presentation in this report. Drs. Bruce and Williams were also kind enough to provide unpublished values for inclusion in the summary of human data during exertion. Dr. Earl Lasher performed the surgery on the dogs and Dean Franklin, Don Baker, and E. J. Klink were in charge of the electronic recording equipment.

SUMMARIO IN INTERLINGUA

Le cameras ventricular es frequentemente distendite usque al maximo quando canes e normal subjectos human es relaxate e in postura recumbente. Etiam le volumine per pulso approcha valores maximal sub iste conditiones.

In postura sedite o erecte, le corde se reduce e le volumine per pulso ventricular ese reducite correspondentemente de accordo con le lege de Starling pro le corde.

Le volumine per pulso se augmenta solmente un pauco sub conditiones de effortio e excede rarmente le valores de controlo pro le postura recumbente. Iste augmentate volumine per pulso es generalmente effectuate per un augmento del ejection systolic, con pauc o nulle contribution per un augmento del distension diastolic.

Un distinction debe esser facite inter 3 conditiones de base pro le quales valores de controlo es obtenite in recereas cardiovascular. Illos es le postura erecte, le postura recumbente, e le stato post-thoracotomia sub anesthesia.

Pro evalutar effectos cardiovascular de effortio in postura erecte, il pare appropriate obtener valores de controlo con le subjecto quiete in postura erecte. Sub iste conditiones le volumine per pulso es plus basse in le condition de controlo que durant e le effortio in le majoritate del casos sed non in omnes. Tamen, un augmento progressive del volumine per pulso non occurre parallel al augmento del intensitate del effortio.

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The study of physiology and pathology within the past half-century has done more to emancipate medicine from routine and thraldom of authority than all the work of all the physicians from the days of Hippocrates to Jenner, and we are as yet upon the threshold.—William Osler, M.D. *Medicine in the Nineteenth Century.* New York Sun, 1901.

Electrocardiogram of the Healthy Adult Negro

By CHARLES R. GREENE, M.D., AND JOHN J. KELLY, JR., M.D.

The T waves of the precordial electrocardiograms are upright in healthy adult white subjects. On the other hand, several reports have drawn attention to T-wave inversion "juvenile pattern" in adult Negroes free of organic heart disease. This study demonstrated no increased incidence of the "juvenile pattern" in healthy adult Negroes. The standards for normality are identical for both white and Negro. When abnormalities of the T wave are found in Negroes, an explanation other than that of race should be sought.

THE T waves of the precordial electrocardiograms of infants and children are usually inverted in leads V_1 to V_4.[1-4] This inversion of the T waves over the surface of the right ventricle is frequently referred to as the "juvenile pattern."[5] As the child ages, the negativity of the T waves in this area diminishes. By maturity upright T waves are found in leads V_3 and to the left in healthy white subjects.[4]

Several groups of investigators have reported the persistence of the "juvenile pattern" in a significant percentage of adult Negroes free of heart disease.[5, 6] Another study could demonstrate no difference between the precordial electrocardiograms of healthy adult whites and Negroes.[7] Because of the importance of establishing normal standards for a healthy Negro population, a reevaluation of this problem was undertaken.

MATERIALS AND METHODS

One hundred and forty-four Negroes varying in age from 18 to 69 were studied. All were free from disease as determined by history and physical examination. This group was composed of hospital employees, nurses, and resident physicians. The majority of the subjects were either native or long-time residents of New York. The dietary histories obtained from this group revealed no evidence of an inadequate diet either at the present or during the past. There were 105 females and 39 males. The age distribution is given in table 1. More females than males were deliberately studied because of the reported higher frequency of the "juvenile pattern" in adult women than in men. The age distribution is about the same in the 2 sexes, 44 per cent of the females and 51 per cent of the males were under 30 years of age.

Standard 12-lead electrocardiograms were taken in the recumbent position 2 or more hours postprandially. The precordial electrodes were placed in accordance with the recommendations of the American Heart Association. All electrocardiograms were recorded on a Sanborn Viso-Cardiette by one or the other of the authors. The subjects appeared to be at ease and not disturbed by the procedure.

RESULTS

The electrocardiograms of the entire group were within the limits of normal. No abnormalities of the QRS complexes or S-T segments were encountered. In tables 2 and 3 are presented the distribution of the electrical axis and position of the hearts in this group of subjects. A normal axis is defined as one that lies between 0° and 90°. Although not indicated in table 2, the degree of axis deviation when present was usually slight. A vertical or semivertical electrical position of the heart was present in 40 per cent of the females and 57 per cent of the males studied. Other observers had noted a higher frequency of the persistence of the "juvenile pattern" in adult Negroes with this position of the heart than with other positions. A high percentage of subjects with the vertical or semivertical position in this population should

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vor a high incidence of T-wave abnormali-
s in this study.

The data pertaining to the T waves of
e precordial leads are summarized in table
Results for both sexes are included in this
ble. Only 1 subject, a 20-year-old girl, ex-
ibited a diphasic T wave in V_3. The T
ave of V_2 was inverted in this same person.
hese results are similar to those found in
ealthy white adults. Inversion of the T
ave of the right ventricular epicardial leads
as been noted to be more frequent in young
omen than in older women or men. All
ubjects with either inverted or diphasic T
aves in V_2 were women between the ages
f 18 and 21 years. Upright T waves in V_1
ere present in 80 per cent of the male sub-
ects but only in 40 per cent of the females.

TABLE 1.—*Age Distribution of the Subjects*

Age	Female	Male
15-19	7	2
20-24	22	10
25-29	17	8
30-34	21	7
35-39	23	4
40-44	11	2
45-49	2	2
50-54	1	3
55-59	1	1
Total	105	39

TABLE 2.—*Electrical Axis of the Heart*

	Female (%)	Male (%)
Right	1	4
Normal	83	86
Left	16	10

TABLE 3.—*Electrical Position of the Heart*

	Female %	Male %
Vertical and semivertical	40	57
Intermediate and indeterminate	51	28
Horizontal and semihorizontal	9	15

DISCUSSION

The term "juvenile pattern" is an expression used to describe the negativity of the T waves in the right precordial leads present in infants and children.[2] As the child ages, right ventricular predominance yields to left ventricular domination, resulting in greater positivity of the T waves of the precordial leads.[1-4]

The T waves are usually upright in all unipolar precordial leads except in V_1 and occasionally in V_2 in healthy adult white subjects.[8] Most electrocardiographic authorities are in agreement that the T waves should be upright from V_3 leftward. Some would allow a negative T in V_2[9] as within the limits of normal, whereas others would not.

Reports of the persistence of the "juvenile pattern" in adult Negroes free of heart disease would seem to challenge both the standards of normality and the usual explanation for the disappearance of the negative right precordial T wave with age. The first of these reports was by Littman, who found an 8-per cent incidence of diphasic or inverted T waves in the CF_4 lead of Negro women and a 3 per cent incidence in Negro men.[5] These subjects were free of heart disease as determined by a clinical examination. Littman offered no explanation for these observations other than that the persistence of the "juvenile pattern" seemed to occur in subjects with a tendency to right axis deviation, thin chests, and small hearts. The high incidence of inverted T waves over the right side of the chest observed by Littman can be explained in part by his use of the bipolar CF leads. In subjects with vertical hearts, the sum of a low precordial T wave and a high T wave in the leg lead should result in a negative value. We have checked this and found it to be true. In more recent reports on the persistence of the "juvenile pattern" in the adult Negro, unipolar leads have been employed.

Grusin in a study of electrocardiograms of African Negroes found no relationship between the electrocardiographic pattern and the electrical position of the heart or the body habitus.[10] In this study, 63 per cent

TABLE 4.—*T-Wave Patterns in the Unipolar Precordial Leads*

	TV_1		TV_2		TV_3		TV_4		TV_5		TV_6	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Inverted	68	47.1	1	0.7	0	0.	0	0	0	0	0	0
Diphasic	6	4.1	5	3.5	1	0.7	0	0	0	0	0	0
Upright	70	48.8	138	95.8	143	99.3	144	100	144	100	144	100

of the 150 hospitalized patients and 22 per cent of 50 apparently healthy African female nurses presented abnormal records. Grusin observed not only inverted T waves in the unipolar precordial leads but also S-T depression and S-T elevation with tall T waves. Clinical and postmortem examinations indicated that the electrocardiographic abnormalities were not due to organic heart disease. Because of the ubiquity of malnutrition in the African, these patterns are probably related to a metabolic or nutritional factor in that author's opinion.

Another report concerning the "juvenile pattern" in adult Negroes emanated from a midwest sanatorium.[6] The subjects of this study were Negro men hospitalized for active tuberculosis. All were said to be anxious, tense, and fearful. Although not stated in the report, most were probably malnourished. Of 131 patients 11 per cent exhibited a "juvenile pattern." This pattern could be accentuated by hyperventilation and relieved by Probanthine and potassium salts. Wasserburger suggested that vagotonia is intimately related to this phenomenon of the "juvenile pattern." The reversal of the inverted T waves in these patients by potassium salts is not unexpected, as this substance will cause both the inverted T waves of children and those associated with organic heart disease to become upright.[11]

The only study comparable to the present one was carried out by Keller and Johnson.[7] Their subjects were medical students and student nurses of Howard University. As in our study, the subjects were healthy, well nourished, and medically sophisticated. These investigators found no inverted or diphasic T waves except in V_1 and V_2. They reported a 1-per cent incidence of inverted and diphasic T waves in V_2, and 47 per cent in V_1. The age range of the subjects varied between 22 to 39 years. Our results would have been nearly identical if we had excluded the subjects in our study under 22 years of age. The 6 individuals of our study with inverted or diphasic T waves in V_2 were women between 18 and 21 years.

It seems clear from our observations and those of Keller and Johnson that there is no electrocardiographic pattern peculiar to the healthy adult Negro. The persistence of the "juvenile pattern" and other reported electrocardiographic changes must be explained in terms other than of race. Indeed we have seen similar patterns in the Apache Indian.[12] Investigation of subjects with the "juvenile pattern" frequently is rewarded with evidence of malnutrition, metabolic disturbance, or anxiety with hyperventilation. It appears probable that a gracile habitus with a vertical heart is not responsible for the persistence of the "juvenile pattern," although it may be a factor. Many of our subjects had this body build; 40 per cent of our female subjects and 57 per cent of the men had either a vertical or semivertical position of the heart.

This study has also confirmed previous observations that inversion of the T waves of the right ventricular precordial leads are more likely to occur in young women than in older women or men.

SUMMARY

Precordial electrocardiograms of 144 healthy adult northern Negroes were analyzed. All curves were within normal limits. No inversion of the T waves was found in

leads V_3 through V_6. One individual exhibited a negative T in V_2 and a diphasic T in V_3. Five instances of diphasic T in V_2 were recorded, all were females between 18 and 21 years of age.

Eighty per cent of adult males presented upright T waves in V_1, whereas in only 40 per cent of the female subjects were T waves positive in V_1.

The T wave of the unipolar precordial electrocardiogram of the healthy, adult American Negro is no different from that of the healthy white adult.

Summario in Interlingua

Esseva analysate electrocardiogrammas precordial de 144 normal adultos negre habitante le nord del Statos Unite. Omne le curvas esseva intra le limites normal. Nulle inversion del unda T esseva trovate in le derivations V_3 a_6. Un subjecto exhibiva un unda T negative in V_2 e un unda T biphasic in V_3. Esseva notate cinque casos de unda T biphasic in V_2. In omnes il se tractava de femininas de etates de inter 18 e 21 annos.

Octanta pro cento del adultos masculo presentava positive undas T in V_1. Le mesme observation aleva pro solmente 40 pro cento del adultos feminin.

Le unda T del unipolar electrocardiogramma precordial de normal adulte negros american non differe ab illo de normal adulte americanos de racia blanc.

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Multiple and Infraductal Coarctations of the Aorta

By Lawrence I. Zaroff, M.D., Isadore Kreel, M.D., Harold J. Sobel, M.D., and Ivan D. Baronofsky, M.D.

With the recent rapid improvements in methods of diagnosis and treatment of cardiovascular diseases, the surgeon today can attempt to cure the unusual as well as the more common types of defects. Refinements in the technics of cardiac catheterization, angiocardiography, grafting, hypothermia, and extracorporeal circulation have been a great stimulus to the description of the rare lesions in the hope that ultimately a completely corrective procedure can be performed. In this paper, a case of multiple coarctations of the aorta is presented and discussed with a review of the literature. To our knowledge this is the first case report in which there have been 4 distinct coarctations of the aorta.

Case Report

The patient was a 32-year-old Puerto Rican woman with a known murmur since the age of 12 and a recent onset of precordial discomfort, dyspnea, and fatigue. No signs or symptoms of congestive heart failure or subacute bacterial endocarditis were evident. Physical examination revealed the following positive physical findings: the blood pressure was, in the right arm 120/90; in the left arm 205/115, and in the right leg 140/100; the right radial pulse was weak, the left was strong, and the femoral pulses were decreased, but palpable. The heart was enlarged to the anterior axillary line in the sixth intercostal space. A grade-II systolic murmur was heard over the entire precordium, loudest along the left sternal border. No collateral pulsations were felt.

Laboratory Findings. The electrocardiogram indicated left ventricular hypertrophy. Radiographic and fluoroscopic examination of the chest showed considerable enlargement of the heart to the left, giving an appearance of left ventricular enlargement. The arch of the aorta showed a shallow impression on its superior posterior aspect and the descending aorta was located unusually far toward the left with the esophagus also somewhat deviated to the left. The configuration of the upper portion of the aorta was somewhat suggestive of the so-called atypical coarctation; however, no narrow segment of aortic arch was visualized, nor was there any evidence of rib notching. Because of the x-ray findings, venous angiocardiography was performed, which revealed a narrowing of the descending aorta in the midthoracic region.

Hospital Course. A diagnosis was made of lower thoracic aortic coarctation with separate occlusion of the right subclavian artery. At surgery a left thoracotomy revealed a marked stenosis approximately 2½ inches below the origin of the left subclavian artery. No inflammation or adhesions were observed surrounding the aorta; however, peculiar calcification of the wall of the aorta was noted distal to the coarctation. The aorta was cross clamped above and below the area of coarctation, whereupon the blood pressure rose to over 300 mm. Hg. This blood pressure elevation was controlled with a slow intravenous drip of trimethaphan camphorsulfonate (Arfonad) until the resection of the coarctation was completed. Upon slow removal of the cross clamps, the blood pressure fell markedly and an infusion of levarterenol (Levophed) was instituted. Over the next 15 minutes the Levophed was gradually slowed as the blood pressure rose to about 200 systolic. As the chest was being closed, ventricular fibrillation developed and persisted despite all attempts at resuscitation.

Postmortem Examination. The pericardium and epicardium revealed several areas of hemorrhage and some fibrin secondary to cardiac massage. The heart weighed 570 Gm., and was markedly enlarged due to hypertrophy of the left ventricle. The right atrium and ventricle were comparatively small, so that they appeared as appendages of the left heart. The tricuspid, pulmonic, mitral, and aortic valve rings measured 9.5, 5.5, 9.0, and 6.0 cm., respectively, in circumference. The right and left ventricular myocardium measured 0.3 and 2.5 cm., respectively, in thickness. The valvular architecture and myocardium were otherwise unremarkable.

The aorta was markedly sclerotic and calcified from the region of the transverse arch distally (fig. 1). There was an old arteriosclerotic occlusion in the right subclavian artery at the bifurcation of the innominate artery. An intact fresh annular suture line was present in the aorta 13 cm. distal to

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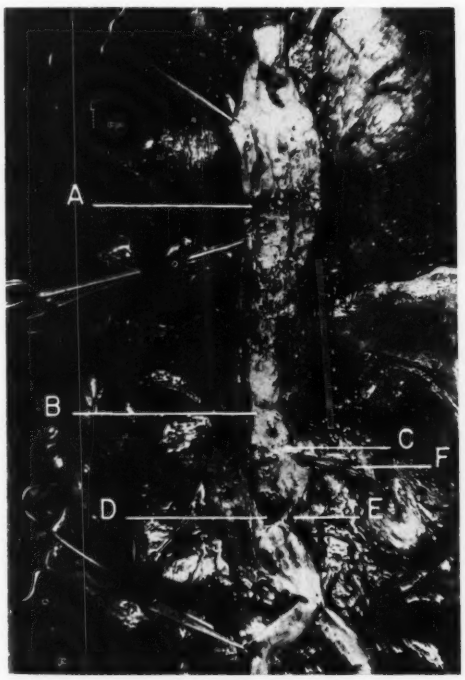
e aortic valve ring at the site of the first coarc-
ion. A small annular cushion producing only
nimal narrowing of the lumen of the aorta was
ted immediately below the orifice of the celiac
tery. A slightly more prominent ridge was found
cm. distal to this area immediately above the
ifice of the right renal artery. The intervening
gment of aorta was slightly dilated. A severe
formity of the aorta with eccentric narrowing of
e lumen produced by a diaphragm-like septum
as found 4.8 cm. distal to the origin of the right
nal artery. The only communication between
e proximal and distal aorta in this region was
channel that extended along the posterior wall
the aorta from a point 1.5 cm. proximal to the
ptum. This channel measured 0.6 cm. in diam-
ter. The segments of aorta distal to the ridge
nd diaphragm were moderately dilated. The left
enal artery was traced to the region between the
idge and diaphragm, where it ended blindly. No
ollateral renal arteries were noted. There was
minimal atherosclerosis distal to the channel. The
liac, right and left common carotid, and left sub-
clavian arteries measured 1.4, 3, 2, and 2 cm.,
respectively, in circumference. The brachiocephalic arteries were markedly sclerotic. The coronary arteries were widely patent throughout, with little sclerosis. There was a dimple in the aortic wall at the site of the ligamentum arteriosum.



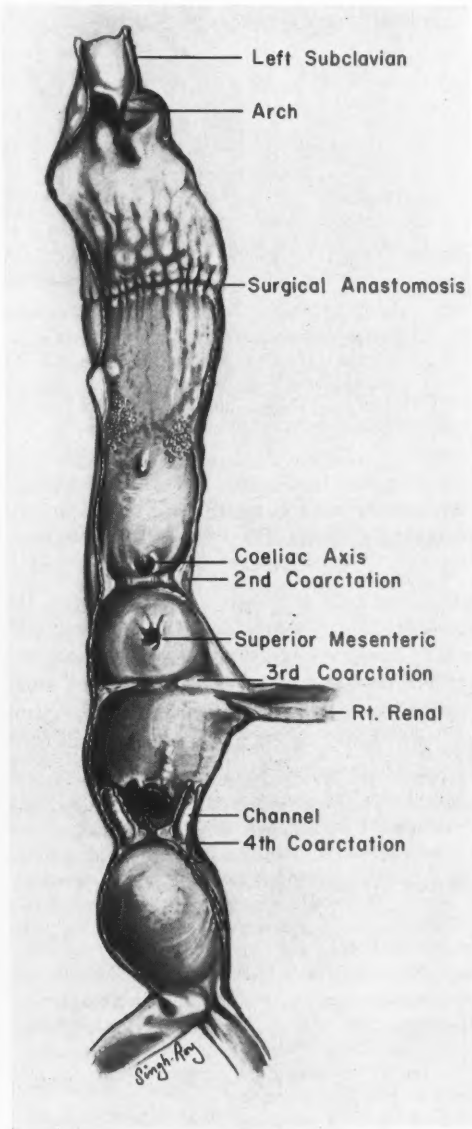


FIG. 1. Photograph (*left*) and drawing (*right*) of aorta opened showing marked atherosclerosis, surgical anastomosis (*A*), 3 areas of coarctation (*B*, *C*, and *D*) channel (*E*), and right renal artery (*F*).

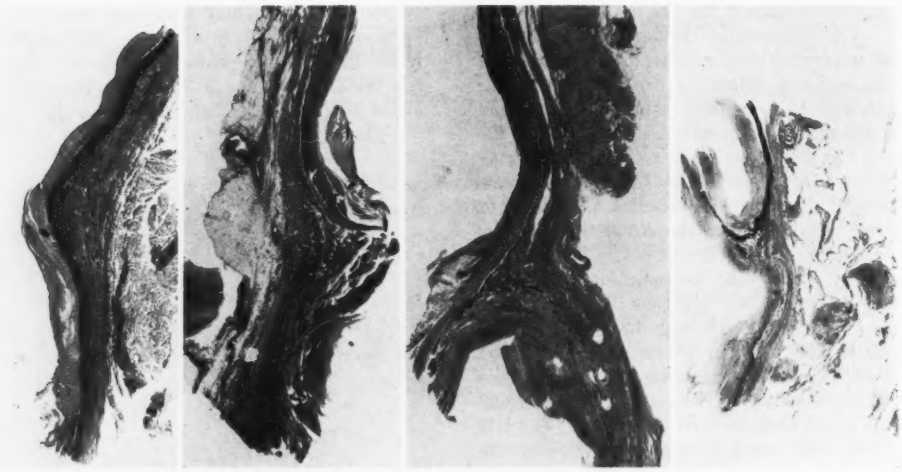


FIG. 2. *First.* Cushion (*B* in fig. 1) showing subintimal fibrosis and thickening of intima and media with abortive infolding. Weigert stain × 4.5. *Second.* Ridge (*C* in fig. 1) showing more marked infolding. Weigert stain × 4.5. *Third.* Distal septum (*D* in fig. 1) showing most marked infolding. Weigert stain × 4.5. *Fourth.* Channel (*E* in fig. 1) showing most marked infolding. Weigert stain × 4.5.

The lungs were partially atelectatic and congested. A few fibrous tags found in the pulmonary arteries were thought to be old organized pulmonary emboli. The liver and spleen were congested. Numerous depressed stellate subcapsular scars and fibrous adhesions were noted over the anterior surface of the liver near the dome of the right lobe. The left kidney weighed 85 Gm. and its surface was smooth. The right kidney weighed 100 Gm. and had numerous vascular scars over the surface.

On microscopic examination the myocardium showed focal scarring. The aorta was markedly atherosclerotic with papillary calcific excrescences in areas. The right subclavian and left renal arteries had old occlusions. On section, small arteries were noted adjacent to the left renal artery. The surgically excised segment of aorta consisted of several fragments showing severe atherosclerosis. The sites of coarctation revealed subintimal fibrous thickening and fragmentation of the elastica. The media was thickened in the region of the proximal cushion, and resembled an abortive infolding (figs. 2–5). The ridge revealed more marked infolding. The distal coarctation and channel revealed infolding and approximation of the media to the most marked degree.

The liver was congested. Numerous granulomata were seen scattered throughout the hepatic parenchyma. These varied from hyalinized nodules to fibrillar nodules some of which contained ova of *Schistosoma mansoni.* Many similar lesions were found in the submucosa of the large and small intestine and lung.

Review of the Literature

Gross[1] has stated that 98 per cent of all coarctations are located in the first segment of the descending aorta just distal to the arch. More recent reports testify to an increasing awareness of coarctations below the isthmus.

Coarctations of the thoracic aorta below the isthmus have been reported as early as 1835, when Schlesinger[2] described a localized narrowed area just above the diaphragm. Another case of a lower thoracic aortic constriction was published by Hasler[3] in 1911. In that report the coarctation was located 3 cm. above the diaphragm, and the aorta was replaced by a fibrous cord for a distance of 2 cm. In 1930 Costa[4] discussed a case with an intra-aortic diaphragm in the lower thoracic aorta. Hickl,[5] in 1931, presented an instance in which there was a cylindrical narrowing just below the isthmus. In 1933, Hahn[6] reported a localized aortic narrowing at the level of the diaphragm. Olim,[7] in 1949, attempted to resect a coarctation below the isthmus. His patient was a 20-year-old girl with a lesion located 5 cm. above the diaphragm. The operation failed be-

cause of lack of a graft to replace the 1.7 cm. area that was resected. Bahnson and co-workers,[8] in 1949, reported a lower thoracic coarctation 4 cm. in length. The only procedure performed was a sympathectomy. In 1950, Freeman and colleagues[9] demonstrated by retrograde carotid aortography, a narrowing of the aorta in the regions of the eleventh thoracic and first lumbar vertebrae. Their patient was a 14-year-old girl with multiple congenital anomalies and a blood pressure of 125/125 in the right arm and 130 in the legs. A successful resection of the lower thoracic coarctation was accomplished by Beattie and associates,[10] in 1951. He resected a 6.5 cm. coarctation above the diaphragm and replaced it with a homograft. Brock and Graham,[11] in 1952, resected a coarctation of the lower thoracic aorta that was associated with an aneurysm above the area of stenosis. Both lesions were removed and replaced with a homograft. Another successful operation was performed by Glenn et al.,[12] in 1952. In their case, the coarctation involved the lower third of the thoracic aorta and the upper abdominal aorta up to the celiac axis. A splenectomy was done and the splenic artery anastomosed to the thoracic aorta above the coarctation. In 1953, Deterling[13] resected a long coarctation of the inferior thoracic aorta and replaced it with a graft with good result. Since then, cases have been described by Depraz,[14] Dubost and Binet,[15] Hulting,[16] and Maurea.[17]

Coarctation of the abdominal aorta is also being seen and reported more frequently. Quain,[18] reported the first case of this type in 1847. His case had a narrowing of the aorta just below the renal arteries. In 1861, Power,[19] described the lesion immediately below the inferior mesenteric artery. Nothing further was published until the 1930's, when papers by Maycock[20] and Baylin[21] appeared describing a stenosis below the renal arteries. In 1941, Steel[22] reported a 46-year-old woman who died of a cerebral vascular accident and at postmortem examination, a marked constriction of the aorta just above, and at the level of the renal arteries, was found. In 1949, Bahnson et al.,[8] published a case in which a preoperative diagnosis of coarctation of the abdominal aorta just below the renal arteries was made by angiocardiography. At operation the aorta was dilated below the diaphragm for several inches and then became quite narrow at the level of the second lumbar vertebra. The adventitia was stripped from the renal artery. The omentum was placed against the left kidney and a bilateral sympathectomy was done. Kondo and associates[23] reported a 12-year-old girl who died in acute pulmonary edema. The abdominal aorta, at autopsy, showed a marked degree of stenosis between the celiac axis and the renal arteries. There was marked arterial sclerosis proximal to the coarctation. Wang,[24] in 1950, reported the case of a 56-year-old man with congestive heart failure who had a coarctation 3 cm. above and at the level of the renal arteries. Doumber and co-workers[25] described the case of a 49-year-old hypertensive patient with intermittent claudication. Aortography showed a stenosis at the level of the renal arteries with visualization of the right, but not the left artery. A left nephrectomy was performed without benefit. Goldzieher and associates[26] described a 45-year-old woman with paroxysmal hypertension who was explored for possible pheochromocytoma, but a coarctation at the level of the renal arteries was found. Fisher and Corcoran[27] recorded a case of a 14-year-old boy with blood pressure of 238/160 in the arm and 256/100 in the left leg. A preoperative aortogram was apparently normal. At laparotomy, the right kidney was smaller than the left and no pulse was palpable in the right renal artery. A right nephrectomy was performed. The patient died postoperatively, and postmortem examination showed a constriction of the aorta at the level of the renal arteries which had only slit-like orifices. The histologic picture was similar to that of congenital coarctation of the isthmus. In 1952, Albanese and Balia[28] operated on a 12-year-old girl who had hypertension in the upper extremities, absent pulses in the abdominal aorta and femoral arteries, and a retrograde aortogram that showed no filling above the renal

arteries. At exploration, the aorta was hypoplastic from the diaphragm to the renal arteries with a markedly narrow area just above the renal arteries. This area was resected and a homograft was inserted, but the patient died postoperatively because of uremia and hypertensive encephalopathy. In 1950, Inmon and Pollock[29] reported on the autopsy findings in a 32-year-old white woman who had a constriction of the aorta just below the renal arteries. A thrombus extended upward from this narrowed point occluding the left renal artery and impinging upon the orifice of the right renal artery. Ritchie and Douglas[30] discussed the case of a 47-year-old man with intermittent claudication, blood pressure in the arm of 140/109, and no femoral pulses. At laparotomy, the aorta was found to terminate at the level of the renal vessels in a pulsatile cul-de-sac. Below this, an atretic tube of 0.5 cm. passed down to bifurcate into 2 narrowed iliac vessels. A bilateral sympathectomy was performed with some improvement. Gerbasi and associates[31] recorded a case in 1958, in which a homograft was successfully inserted to bypass a coaretation in the region of the celiac axis. Their patient was an 11-year-old girl with hypertension in the upper extremities and decreased femoral pulsations. An angiocardiogram was interpreted as showing a typical coaretation but at thoracotomy the coaretation was felt lower down. Postoperatively, a retrograde aortogram showed a coaretation 2 to 3 cm. above the renal arteries. At a second operation, the graft was successfully inserted.

Multiple coaretations are indeed rare lesions and, to our knowledge, there are reports of only 7 cases in the literature. In each case, the coaretation consisted of 2 areas of stenosis. In 1937, Benkwitz and Hunter[32] reported the case a 67-year-old man with hypertension who died of pneumonia. No mention was made of the femoral pulses. At postmortem examination, 2 definite constrictions were found. The aorta became constricted at the beginning of the transverse arch and reduced to a diameter of 1 cm. at the site of the infantile isthmus. Two centimeters distal to the first coaretation, the descending aorta presented an annular constriction with almost complete obliteration of the lumen by diaphragm. The ligamentum arteriosum was located at the site of the second coaretation. In their article Benkwitz and Hunter discussed 3 previously described similar cases.[33–35] In these cases the aorta was first constricted immediately beyond the origin of the left subclavian artery with a second area of stenosis at the level of the closed ligamentum arteriosum. Brock,[36] in 1953, reported the case of a 17-year-old girl whose aortogram revealed what was apparently the usual type of coaretation. However, at thoracotomy a second area of stenosis was seen, 1 cm. above the main coaretation. The lower lesion was narrower than the upper. Between the 2 coaretations the aorta was thin and bulging. Both lesions were resected and a homograft was successfully inserted. No description was given of the microscopic pathology. In 1955, Cooley and DeBakey[37] reported a 35-year-old man with a blood pressure of 260/160 in the left arm and no detectable pressure in the left leg. At operation, a constricting lesion, which began in the lower third of the descending thoracic aorta and extended a distance of 8 cm., was excised and replaced with a homograft. The constriction was surrounded by scarring and fibrosis. Because the leg pulses remained weak following surgery, retrograde aortography was performed. This showed a constriction in the proximal abdominal aorta just above the superior mesenteric artery and occluding the celiac artery. At a second operation this constriction, also atherosclerotic and calcified, was excised and replaced with a second homograft. A recent report of a double coaretation is that of Geronimo and associates.[38] Their case was an 11-year-old girl with a blood pressure of 260/120 in the right arm, 160/130 in the left arm, and no femoral pulses. Previously the blood pressure in the left arm had been completely absent. He attributed the changes in pressure to occlusion and recanalization. An aortogram revealed a long constriction in the lower thoracic aorta and a second area of narrowing in the ab-

dominal aorta above the superior mesenteric. Between the 2 constrictions, the aorta was dilated. Both segments were resected and successfully replaced with a homograft.

Discussion

The work of Edwards and associates[39] has led to the belief that the usual type of coarctation is due to a developmental defect of the media of the aorta. A localized medial thickening occurs as the primary lesion. In older patients a secondary intimal thickening may also occur. The microscopic findings in our case are perfectly consistent with the diagnosis of multiple congenital coarctations of the aorta. The occurrence of severe atherosclerotic changes and calcification proximal to an area of stenosis is well documented.[20, 23, 40] Unfortunately, many of the cases of lower aortic stenotic lesions reported in the literature do not include a precise description of the histologic findings. The majority of the stenosing lesions in the descending thoracic aorta are of the long tapering variety. Their appearance has in general been considered by most authors as compatible with acquired inflammatory changes.[3, 5, 8, 13] The more localized lesions without evidence of inflammation have been thought of as congenital in origin.[4, 6, 7]

Narrowing of the abdominal aorta may occur in any region, but commonly is either below or at the level of the renal arteries. These lesions for the most part, have been regarded as congenital in origin.[8, 20, 23, 27]

The 4 initially reported cases of double coarctation were similar.[32, 35] They consisted of constricted areas localized immediately beyond the origin of the left subclavian and at the level of the ligamentum. They were probably of congenital origin. Brock's[36] case also resembled these early reports. Cooley and DeBakey[37] felt that in their case each of the constrictions was acquired. These lesions were arteriosclerotic and calcified and surrounded by scarring and fibrosis. They believed the etiology was a localized aortitis resulting in segmental arteriosclerosis with obliteration of the aortic lumen. In Geronimo's[38] case, the aorta was surrounded by dense inflammatory adhesions. The stenotic areas corresponded to deposits of granulation tissue in the media. The authors believed that the lesions were essentially an inflammatory destruction of the media.

Diagnosis and Treatment

The diagnosis of lower thoracic or abdominal coarctation should be suspected in any patient with relative hypertension in the upper extremities who, in addition, has evidence of increased collateral circulation over the lower chest, back, or abdomen. Murmurs, pulsations, or thrills in these regions should alert one to the possibility of an atypically located coarctation.[2, 9, 31, 41] In uncomplicated coarctations, intermittent claudication occurs in 8 per cent of the cases,[41] but apparently is of greater incidence in abdominal coarctations, occurring in approximately one third of the cases.[29] In typical coarctations, the aortic knob is small and may be absent.[42] When the coarctation is in the lower thorax or abdomen, the aortic knob is normal and notching may be present only in the lowest ribs. If any of the above signs or symptoms are found, we consider it is vital to delineate the exact site of the coarctation, with thoracic and abdominal aortograms. Intravenous angiography has resulted in misinterpretation of aortic lesions because of dilution of the dye.[31] Particular attention should be paid to the length of the lesion and its relation to the renal arteries, for this will determine the operative procedure. Resection and grafting, bypass procedures, or even separate perfusions of the renal arteries,[43] might be necessary. It is not inconceivable that all 4 lesions in our case might have been successfully resected had we recognized them.

Summary

Reports of multiple and infraductal coarctations are appearing more frequently in the literature as interest in the treatment of cardiovascular disease grows.

A case with 4 distinct coarctations is presented.

SUMMARIO IN INTERLINGUA

Reportos de coaretationes multiple e infraductal del aorta deveni de plus in plus frequente in le litteratura con le crescentia del interesse pro le tractamento de morbo cardiovascular.

Es presentate un case con 4 distincte coaretationes.

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The great republic of medicine knows and has known no national boundaries, and post-graduate study in other lands gives that broad mental outlook and that freedom from the trammels of local prejudice which have ever characterized the true physician.—William Osler, M.D. *The Importance of Post-Graduate Study.* Lancet, 1900.

Aberrant Left Coronary Artery

Report of a Case and Review of the Literature

By HARVEY COHEN, M.B., B.CH., AND SHIRLEY SIEW, M.B., B.CH.

RECENT advances in the successful surgical treatment of a number of congenital heart diseases have stressed the importance of diagnosis as a first prerequisite to proper management. Rosenbaum,[1] in a recent article deprecated the continued use of "idiopathic hypertrophy of the heart" as a nondescript term for heart conditions in infancy and early childhood, characterized by congestive cardiac failure, normal blood pressure, absence of cyanosis and murmurs, and without evidence of a shunt.

The anomalous coronary artery was included in this group in the past. In 1911, Abrikosoff[2] first described the existence of this anomaly; and in 1933, Bland, White, and Garland[3] made the first antemortem diagnosis of this condition. Up to now 45 cases have been reported.[2–37]

CASE REPORT

An African male infant, aged 9 months, was admitted to the hospital because of coughing and restlessness for 2 weeks. He had been born normally after an uneventful pregnancy and appeared healthy at birth.

On physical examination he was in obvious distress, restless, and dyspneic. He was underweight and small.

The left side of the chest bulged prominently, and moved less than the right side, which was resonant and in which the breath sounds were normal. The area of cardiac dullness was increased and there was dullness at the left base. Breath sounds were diminished at the left base and fine crepitations were audible over the lower half of the chest posteriorly.

The heart was enlarged. The maximum cardiac impulse was in the fifth intercostal space in the anterior axillary line. No thrills or murmurs were observed. The heart sounds were clearly audib and apart from a tachycardia the rhythm was no mal.

The abdomen was slightly distended, and th liver edge was palpable about 3 cm. below th costal margin.

X-ray of the chest revealed a grossly enlarge heart with "fairly" good pulsation. The enlarge ment appeared mainly left ventricular, and th left border of the heart gave the impression of a aneurysmal dilatation of the left ventricle. N abnormal calcifications were noted.

Examination of the blood revealed a hemoglobi of 9.7 Gm. per cent, 33,200 leukocytes per mm.³ with 92 per cent neutrophils.

Electrocardiogram showed regular sinus tachy cardia of 200 per minute, deep Q waves in leads I, aV_L and V_5 and V_6, and inverted T waves in leads I, II, and aV_L (fig. 1).

The patient had several episodes of crying and restlessness, accompanied by dyspnea and sweating, particularly after feeding. Between attacks he was happy and interested, playful, and amenable to examination and handling. He died suddenly 14 days after admission.

Morbid Anatomy of the Heart. The heart weighed 125 Gm. or 3 times the normal weight of 39 Gm. at 9 months. The left ventricle occupied at least three quarters of the anterior surface of the heart and showed a globular enlargement (fig. 2, table 1).

The pericardium was smooth and glistening. The aorta and pulmonary artery were normal. The right coronary artery arose normally from an ostium 2 mm. in diameter from the anterior aortic sinus (fig. 3 *Left*) and was normally distributed to the right ventricle and posterior half of the left ventricle. No other ostial openings were seen in the root of the aorta.

The left coronary artery originated from the pulmonary artery from a small ostium 1 mm. in diameter, situated in an extremely low position in the sinus of the right anterior cusp (fig. 3 *Right*). From its origin in the pulmonary artery, the left coronary trunk ran inferiorly along the anterior surface of the right ventricle and down the anterior interventricular sulcus to the incisura apicis cordis, where it bifurcated, one branch running antero-

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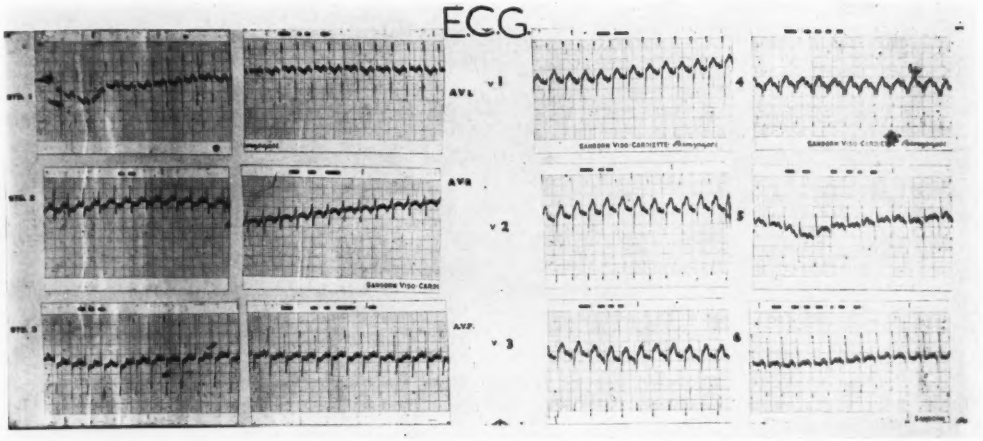

FIG. 1. Electrocardiogram.

inferiorly toward the apex, while the other swept posteriorly to supply the apical portion of the right ventricle. This main trunk thus followed the distribution of the anterior descending branch of the left coronary artery. A large branch followed the course of the left circumflex artery and arose 4 mm. from the root of the pulmonary branch. Several other smaller branches also supplied the anterior surfaces of the left and right ventricles.

The cavity of the left ventricle was greatly dilated with bulging of the anterior wall and displacement of the interventricular septum to the right. There was hypertrophy with thinning in the apical portion. The endocardium showed marked fibrosis, particularly in the anterior wall and interventricular septum. The myocardium was pale with atheromatous degeneration of the apices of the posterior papillary muscles. The endocardium of the left atrium was also grossly thickened and opaque.

The cavity of the right ventricle was diminished by the displacement of the interventricular septum, but the endocardium and the myocardium were normal. All valves were normal, and there was no other congenital abnormality.

Injection of Barium Sulfate into the Coronary Arteries. Although the heart had already been incised moderately adequate injection of the aberrant left coronary artery was achieved. The right coronary artery had been cut just beyond its origin and only the proximal segment could be filled properly. Radiographic photographs of the injected heart showed a very rich vascular network arising from the left coronary artery, supplying the anterior wall of the left ventricle and the apex of the heart. The trunk of the right coronary artery could be seen and anastomoses between its proximal branches and those of the anomalous left coronary artery were demonstrated.

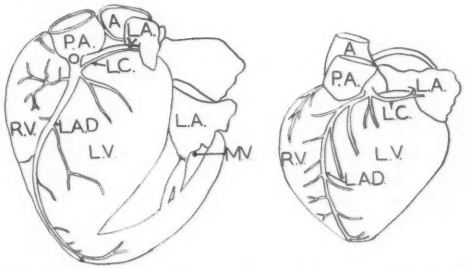

FIG. 2. General size, configuration and appearance of the anterior surface of the heart of the case (A.M.) and that of a normal African male infant 10 months old. *A*, aorta; *P.A.*, pulmonary artery; *O*, origin of aberrant left coronary artery from the pulmonary; *L.A.D.*, anterior descending branch of the left coronary artery; *L.C.*, left circumflex; *L.V.*, left ventricle; *R.V.*, right ventricle; *L.A.*, left atrium; *M.V.*, mitral valve.

In the case of the normal control, the heart was injected and photographed before it was cut. The vascular branches were smaller and formed a fine network, in which relatively few anastomoses could be discerned.

Histopathology. Sections of the anterior wall of the left ventricle showed marked para-arterial fibrosis of the myocardium (fig. 4). In addition there were large areas of diffuse fibrosis, identical in appearance to an organized myocardial infarct. Calcification was seen in some of these areas (fig. 5).

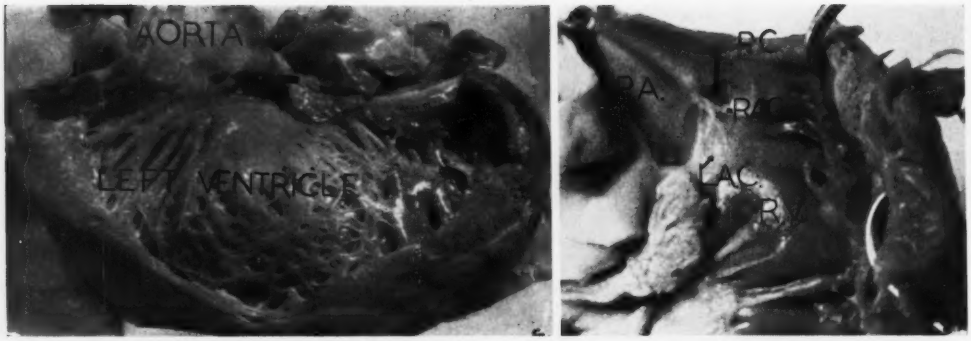

FIG. 3. *Left.* Origin of the right coronary artery. The arrow points to the ostium of the right coronary artery, which is situated normally in the anterior aortic sinus. Marked dilatation of the left ventricle with fibrosis of the endocardium is present. *Right.* Origin of the left coronary artery from the right anterior sinus of the pulmonary valve; *P.A.*, pulmonary artery; *P.C.*, posterior cusp of the pulmonary valve; *R.A.C.*, right anterior cusp; *L.A.C.*, left anterior cusp; *R.V.*, right ventricle. *Arrow*, small ostium situated in the left inferior corner of the right anterior sinus of the pulmonary valve.

The myocardial fibers showed evidence of degeneration—some were vacuolated and others had progressed to recent coagulative necrosis. Irregular cleft-like spaces lined by endothelial cells were seen especially in the more viable parts of the myocardium (fig. 6). They conformed to the description of embryonic sinusoids.

The endocardium of the left ventricle showed an increase of fibrous tissue and a parallel increase of elastic tissue. The larger branches of the abnormal left coronary artery were well formed (fig. 7). The walls of the smaller branches were thinner and had less muscle and elastic tissue than the branches of the right coronary artery. Some of the small arterioles, particularly those in the more fibrosed areas, showed endothelial hyperplasia and a few were almost completely occluded by endarteritis.

The right ventricle and the right coronary artery were normal.

DISCUSSION

Pathogenesis. The anlagen of the coronary arteries are seen first as outpouching endothelial buds in the wall of the aortic bulb, before the spiral septum of the truncus arteriosus develops and separates the aorta and the pulmonary artery.

Abrikosoff,[2] reported the first case of this abnormality and suggested that the anomaly could arise if the primitive bud of the left coronary artery were displaced anteriorly or if there were posterior displacement of the septum. Displacement of the septum would disturb the relative position and size of the aorta and the pulmonary artery. No such evidence was seen in any of the infant cases of the anomalous left coronary artery. The only instance of malposition of the septum together with an aberrant left coronary artery was reported by Konstantinowitsch[38] in a 2-day-old girl who had a grossly malformed cor biloculare with a rudimentary stenosed aorta. One must postulate therefore that this lesion is due to displacement of the primitive bud of the left coronary artery.

In the reported cases[2-37] the aberrant coronary artery was the sole congenital abnormality except for a patent ductus arteriosus in 2 cases,[25, 31] patent foramen ovale in 1 case,[36] and narrowing of the aorta in 2 cases.[18, 37] The course, distribution, and branching followed that of the normal left coronary artery, but the extent of the vascular network varied from less than half of the heart[7] to the entire left ventricle plus a portion of the right ventricle.[26]

The right coronary artery in its origin, course, and distribution was normal throughout.

Pathology. The morbid anatomy of the heart in our case was quite typical with its

TABLE 1.—*Cardiac Measurements after Fixation (cm.)*

	Heart of case A.M.— 9 months	Heart of normal control— 10 months
Weight in Gm.	125	40
Left ventricle:		
Transverse diameter	7.2	5
Longitudinal diameter	5	3.2
Length of posterior surface	5.7	4
Thickness of myocardium		
base	0.8	0.6
Mid ventricle	0.8	0.6
Apex	0.4	0.4
Left Atrium:		
Length of posterior surface	2	1.2
Thickness of myocardium	0.35	0.2
Right ventricle:		
Length of posterior surface	5.5	4.1
Thickness of myocardium		
base	0.3	0.2
Mid ventricle	0.2	0.15
Apex	0.15	0.1

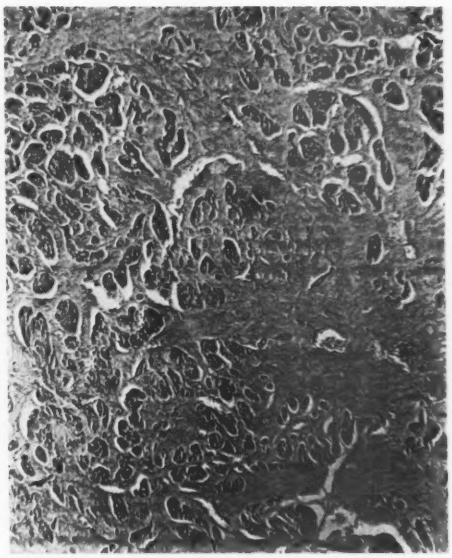

FIG. 4. A section of the wall of the left ventricle showing well-marked para-arterial fibrosis.

characteristic left ventricular hypertrophy. This reached aneurysmal proportions in 12 of the 45 cases.[2, 5, 6, 8, 13, 15, 17, 18, 20, 23, 29, 30] Vivas-Salas[39] considered this abnormality to be a most important cause of cardiac aneurysm in early life. Marked fibrosis particularly in the anterior wall and the interventricular septum may lead to extreme thinning and rupture.[28, 31] Thrombi were present in this dilated, fibrosed cavity in 4 cases.[5, 7, 12, 33] The papillary muscles, being farthest from the blood supply, may show evidence of severe ischemia: yellow-gray patches of degeneration,[25] as were present in our case; atrophy,[36] gray-white scars,[35] fibrosis,[20] replacement by a fibrous band.[23]

The valves were usually normal but the mitral valve was thickened in 1 case,[16] thickened and stretched in another,[30] and showed verrucous projections due to an increase in the myxomatous ground substance in a third.[36]

Histologically, well marked para-arterial fibrosis, organized and recent myocardial necrosis, foci of calcification (54 per cent), persistence of embryonic sinusoids (33 per cent), and sclerotic and endarteritic vascular changes in the smaller branches of the left coronary (33 per cent) were frequently observed. A marked increase of subendocardial fibrous and elastic tissue may be present.

As a result of the anomalous origin of the left coronary artery from the pulmonary artery, the left ventricle receives blood of low oxygen saturation and at the low pressure of the pulmonary circuit. It suffers from anoxemia which causes parenchymatous degeneration of the muscle fibers and condensation of the fibrous tissue, particularly in the para-arterial zone. This is followed by necrosis and fibrosis. Heitzmann[5] first observed the similarity between this lesion and that of coronary occlusive disease in the adult. Fisher and Lloyd[29] noted fibrous tissue surrounding individual muscle fibers and stated that this appearance was quite distinct from that of adult ischemic fibrosis, in which one sees islands of surviving muscle in a sea of fibrous tissue. But most workers agree that these lesions are essentially similar, being only more widespread and of greater magnitude in infants. Myocardial calcification, which is rare in adult occlusive coronary lesions, was seen

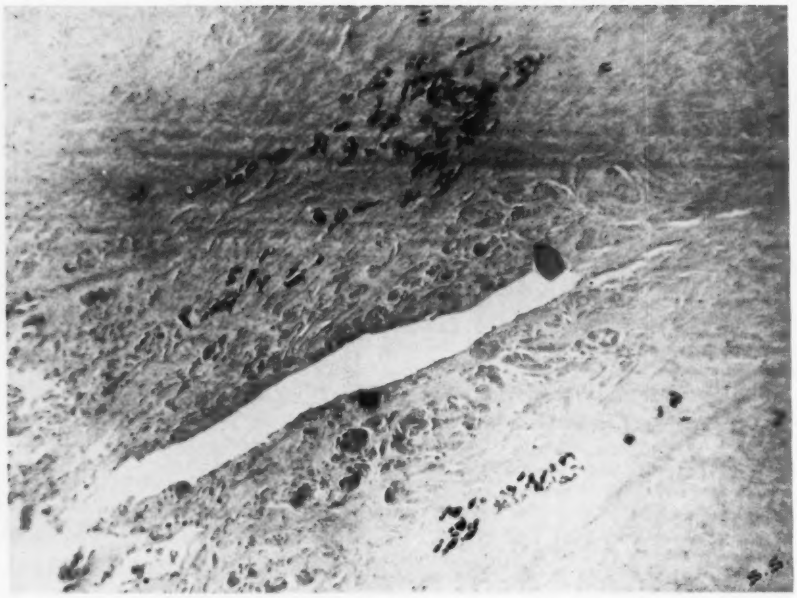

FIG. 5. Dark foci of calcification in an area of dense fibrosis.

in 54 per cent of cases of the aberrant left coronary artery and was believed by Soloff[19] to be pathognomonic in the radiologic diagnosis of this abnormality. Abrikosoff[2] suggested that it followed the necrosis of the muscle fibers, and its prevalence in infants has been ascribed to the relatively higher content in infant myocardium of inorganic calcium, phosphorus, and phosphatase.

Barnard[17] quoted Barcroft's[41] work on the fetal circulation and suggested that this abnormality caused anoxemia of the left ventricle during fetal life. The persistence of embryonic structures such as the sinusoids supported this contention.[20] Taussig[42] did not accept these conclusions and maintained that there is little or no difference in the oxygen content of the blood in the 2 sides of the heart in utero. Kaunitz[23] concluded that coronary ischemia does not manifest itself before birth, since advanced degenerative cardiac changes are not present in infants dying in the immediate neonatal period in whom both coronaries originate from the pulmonary artery.[37, 44, 45] Bassis and Sheinkopf[36] thought that the high intraventricular pressure in fetal life would assure the myocardium of an adequate supply of oxygenated blood.

Clinical Features. In cases with an aberrant right coronary artery originating from the pulmonary artery there is no evidence of functional disturbance or early death. Four such cases[46–49] all lived until adulthood; one died at age 74. This longevity indicates that venous blood would appear to be adequate for the nutrition of the right ventricle, but not for that of the left side.[15] It may still be sufficient for the demands in early infancy, but will fail with the increase of growth and activity of the patient.

The degree of disability and the length of the life span of the individual depend firstly upon the extent of the vascular network from the anomalous vessel—if this is extensive as in Craig's[26] case, the subject dies in early infancy (2 months); if less than half of the heart is supplied by the left coronary artery,[7] then there is relative longevity (10 months). This conclusion is also supported by some of the adult cases, e.g., a man aged 27, in whom the abnormal left coronary artery supplied less of the heart than usual.[50] The second

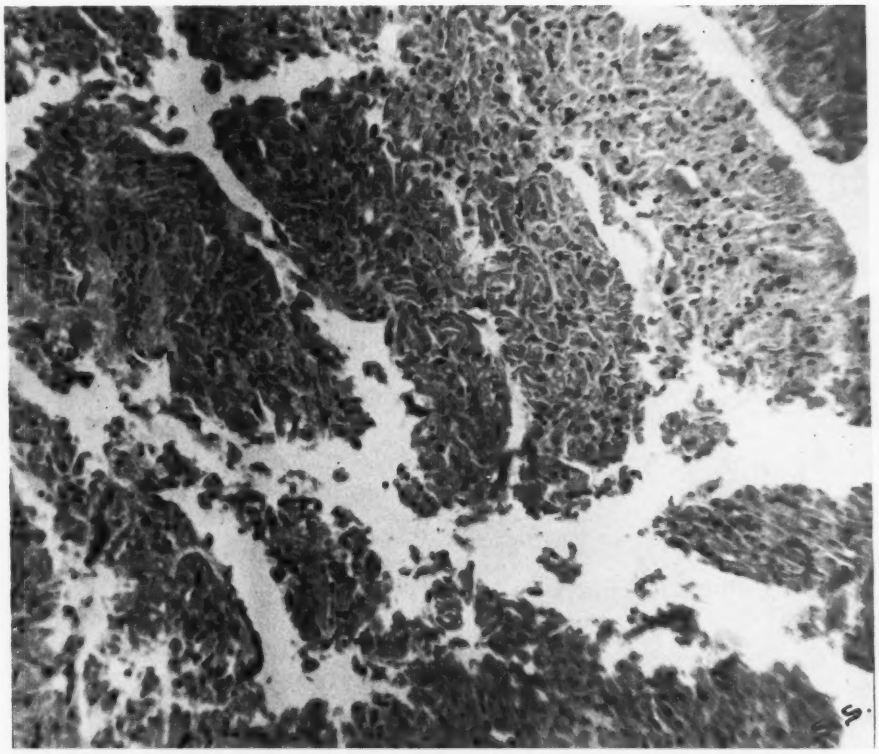

FIG. 6. Persistence of embryonic sinusoids—in such areas the myocardium remains viable.

factor determining the length of survival, is the extent of the collateral circulation from the normal right coronary artery. This may in turn depend on the congenital inherent pattern of distribution of the coronary arteries,[30] or may be determined by pressure gradients in these hearts.[27, 51, 52] Anastomoses were demontrable in most of the 8 adult cases reported, but their presence was variable in the infants of this series.

In the 45 previously reported cases there was a preponderance of female children; the sex was stated in 41 instances, 27 of which were female. The age at which the lesion became evident ranged from 7½ weeks to 13 months. In only 1 case was the infant born prematurely.[22]

Maternal health had been normal in all except 3 instances—one had eclampsia,[20] another syphilis,[22] and the third had amenorrhea for 2 years before pregnancy.

The onset of symptoms was usually delayed, except in 1 case[22] in which a persistent cough appeared at 1 week of age.

The usual presenting symptoms were cough and dyspnea; difficulty with feeding (refusing feeding, vomiting, discomfort and restlessness after feeding; difficulty in swallowing; failure to thrive; sweating); and anginal attacks.

Anginal Attacks. Bland, White, and Garland[3] first drew attention to this condition and the similarity between the attacks of restlessness, sweating, and crying and attacks of angina as seen in adults. These attacks may be precipitated by the effort of feeding. The apparent feeling of well-being and amiability between attacks is in marked contrast.

Electrocardiographic Changes. Since the first description by Bland and co-workers[3] most authors have confirmed the findings of inversion of T waves in all 3 standard leads and low voltage. In the present case T-wave

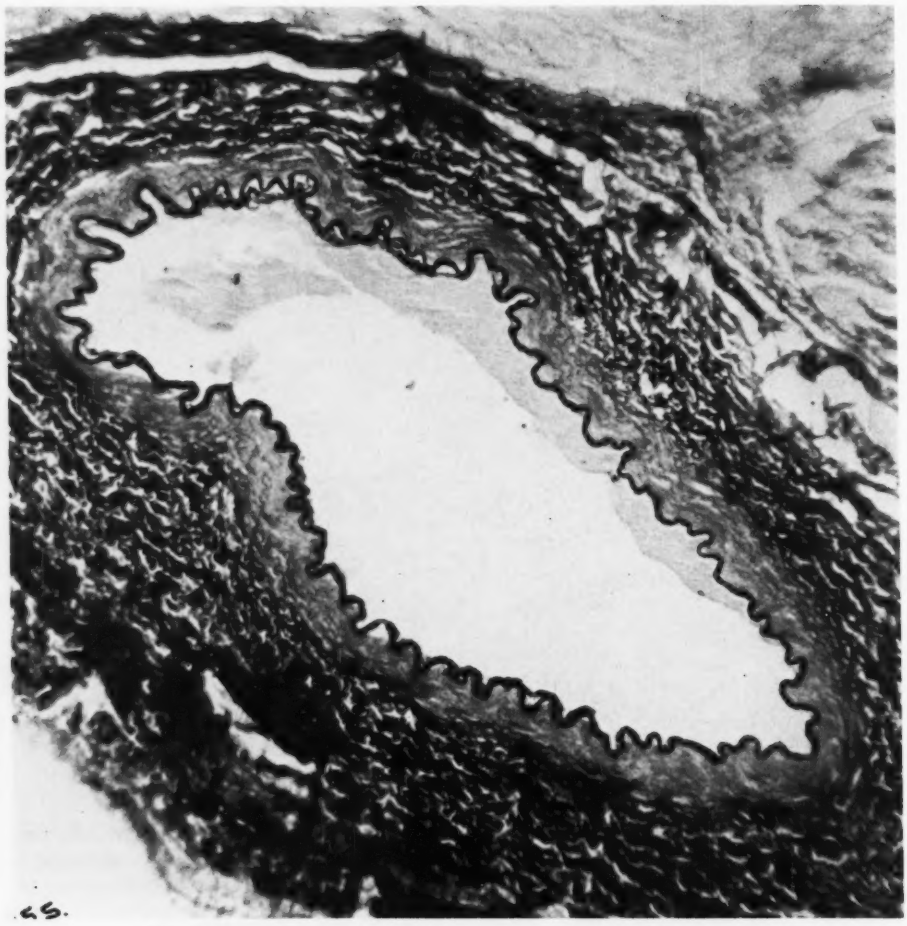

FIG. 7. Large branch of left coronary artery. Weigert-van Gieson stain.

inversion was noticed in leads I, II, and aV_L, and the voltage was high. Deep, wide Q waves were present in leads I, aV_L, V_5 and V_6.

Delayed Onset of Symptoms. Usually the symptoms were delayed until the third month of life. This delay may be due to the patent ductus arteriosus which allows the pulmonary artery to receive oxygenated blood from the aorta. When the ductus closes off, only venous blood reaches the left coronary and myocardial ischemia results.

In the present case, no history of previous attacks was obtained from the mother who appeared to be a reliable and intelligent informant. It follows, therefore, that if the attacks of dyspnea, restlessness, and sweating, seen in hospital, were the first experienced by the patient, then the onset of symptoms in this case was delayed until 9 months of age.

Diagnosis. The diagnosis of this condition should be considered in all cases of congestive cardiac failure in infancy in which cardiomegaly is not associated with cyanosis or murmurs, with no evidence of a shunt, and with normal blood pressure.

Among the other conditions which may show these features are glycogen storage dis-

ease, congenital fibroelastosis, medial necrosis of the coronary arteries, and idiopathic myocarditis.

The radiologic features suggestive of the anomalous left coronary artery are gross cardiac enlargement affecting mainly the left ventricle and poor pulsation on fluoroscopy with a difference in the force of contraction of the 2 ventricles. The gross hypertrophy and size of the left ventricle may suggest aneurysmal dilatation.

Electrocardiograms suggest varying degrees of myocardial ischemia. Several patterns have been recorded, particularly inversion of T waves in all 3 standard leads together with low voltage.[3, 42]

Course. While the anomalous left coronary artery has been reported in 8 adult cases, by far the majority of cases prove fatal in the first year of life. The average age of death in the 45 infant cases reviewed was 4 months.

Treatment. Medical treatment is essentially of a palliative nature and is designed to prevent attacks by the avoidance of those factors which may precipitate these attacks. Sedation is used to relieve the attack.

There has as yet not been any report of surgery to relieve the condition. Procedures have been suggested to increase the supply of oxygen to the left ventricle. Gasul and Loeffler[25] suggested a Potts-Smith operation, in which the left or right pulmonary artery is anastomosed to the descending aorta. Keizer and Rochat[32] thought that the left pectoral artery could be used, and Blalock[53] suggested anastomosis with the internal mammary. Omentopexy might also be considered. McKinley et al.[28] favored the Potts-Smith operation, but objected to Beck's pericardial anastomosis for fear of the development of constrictive pericarditis.

The necessary prerequisite to any proposed treatment is the confident diagnosis of the condition during life. Bland et al.[3] made the first antemortem diagnosis of this condition, and it has been diagnosed clinically 5 times since.[21, 22, 24, 25] (cases 1 and 4)

Summary

A case is reported of the anomalous origin of the left coronary artery from the pulmonary artery in a Bantu male infant aged 9 months. The clinical, radiologic, and electrocardiographic findings, and the cardiac pathology are presented.

The 45 cases previously reported in the literature are reviewed and the clinical syndrome and pathologic physiology of the aberrant left coronary artery are discussed.

Acknowledgment

We are indebted to Drs. M. Tonkin and H. Falcke for permission to publish the case; to Dr. J. Kaye and Miss Dreyer for radiographic assistance; to Miss E. E. A. Gygax for the translation of the German literature; to Mrs. T. E. Lawrence and Mrs. J. E. Bailey for secretarial assistance, and to Miss M. J. H. Barnard for the microscopic sections.

Summario in Interlingua

Es reportate un caso del origine anormal del arteria coronari sinistre in le arteria pulmonar. Le patiente esseva un infante mascule de 9 menses de etate de racia bantu. Le constatationes clinic, radiologic, e electrocardiographic e le pathologia cardiac es presentate.

Es presentate un revista del 45 casos previemente reportate in le litteratura. Le syndrome clinic e le physiologia pathologic del aberrante arteria coronari sinistre es discutite.

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I cannot say that I am in the slightest degree impressed by your bigness, or your material resourses, as such. Size is not grandeur, and territory does not make a nation. The great issue, about which hangs a true sublimity, and the terror of overhanging fate, is what are you going to do with all these things?—Thomas H. Huxley. *American Addresses with a Lecture on the Study of Biology*. London, MacMillan and Co., 1877, p. 125.

Supplemental Value of the Intracavitary Electrocardiograph in Cardiac Catheterization

By Robert B. Dickerson, Col., M.C., U.S.A., and
Timothy N. Caris, Lt. Col., U.S.A.F. (M.C.)

Characteristic intracavitary electrocardiographic complexes at various sites within the heart in normal individuals have been described previously. The intracardiac tracings in 150 catheterizations, 129 of which were abnormal hearts, predominantly congenital defects, were studied in relationship to the position within the heart as determined fluoroscopically. In our experience, the tracings remain sufficiently unchanged in abnormal hearts so that the intracavitary electrocardiogram may be used successfully as a guide, making it possible to decrease total x-ray exposure time considerably. In addition, the significance of an intracavitary injury current became apparent. A few diagnostically useful variants were found and are described.

DURING the last 2 years, intracavitary electrocardiography combined with cardiac catheterization has become an increasingly useful procedure in our hands. Reports are available describing the rather characteristic complexes obtained at various sites in the normal heart,[1-7] and others indicate the possible value of such tracings in specific cardiac abnormalities.[8-11] In our studies in 150 cases, 129 of which were abnormal, it has become apparent that, as a rule, the characteristic tracings at the various sites within the heart,[1, 2, 5] continue to be present.

The intracavitary electrocardiogram refers to the tracing that is recorded as a V lead through an electrode ring affixed to the distal tip of the cardiac catheter. The advantages resulting from its use may be described in terms of increased safety to the patient and the additional information gained.

Increased Patient Safety

Particularly prominent at this time is the diminution in x-ray exposure time required for the usual cardiac catheterization. Whereas a total fluoroscopy time of 10 to 15 minutes was previously accepted as an inherent part of the procedure, it is now possible to complete the entire examination in a total of 1 to 3 minutes of fluoroscopy time in most cases. This is because one can recognize the position of the catheter tip in various chambers of the heart by the intracavity electrocardiogram. It follows that direct fluoroscopic observation is required infrequently during the procedure. Occasionally when the tip is at the junction of the subclavian and innominate veins (when an arm vein is being used) it may be passed blindly upward into the neck unless directly observed. This deviation is readily recognizable, however, since the intracavitary lead assumes the form of aV_L. On such occasions, fluoroscopy may be needed to redirect the catheter. Fluoroscopy is also necessary when the tip of the catheter fails to pass directly out of the right ventricle into the pulmonary artery and further manipulation is required. Except for these instances, the recognition of the catheter tip's position and its passage within the heart is practicable with intracavity electrocardiogram and the simultaneously viewed pressure record. Customarily, these are inspected on a monitoring oscilloscope during the actual procedure.*

Beginning in the superior vena cava, a pattern is recorded remarkably similar to

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*An inexpensive 2-channel monitor can be assembled for less than $100.00 by combining a single-beam oscilloscope with a Heathkit electronic switch.

that of the proximal right atrium except for the generally lesser amplitude of the complexes (fig. 1). Subsequently, in the proximal, mid, and distal right atria, distinctive patterns are inscribed although the pressure records from all points within the atrium are identical. If the catheter tip should enter the coronary sinus, this too becomes apparent in the intracardiac lead. The P-R interval is appreciably shorter with the peak of the P wave appearing later than the peak of the P wave in lead II or that of the right atrial tracing. In contrast to the right atrial pattern, the T waves are upright or occasionally flat. Correspondingly, in the passage through the right ventricle, distinctive patterns are encountered although the pressure waves are of essentially constant form. Once the tip of the catheter is in the pulmonary artery, there is a progressive lessening of amplitude that labels the tracing as extracardiac. Whether the catheter tip is in the proximal or distal pulmonary artery becomes clearly evident from the progressively diminishing size of the complexes.

A further increase in safety to the patient results from reduction of arrhythmias. It has been most impressive to observe how frequently an injury current may be recorded by the intracavity electrode while a concurrently normal complex is inscribed by the conventional lead II monitor (fig. 2*a*). Previously we attempted to recognize injury currents during the procedure from a V_1 lead, but this is far less sensitive and further complicates handling of the patient and equipment. If such an injury current is not heeded and the catheter tip is allowed to remain in the position from which it is generated, disturbances in rhythm frequently make their appearance or become much more severe within the ensuing few minutes. It would appear logical to assume that at such a time, the tip of the catheter is either impinging directly on the ventricular endocardium or else is lodging among the interdigitations of the trabeculae carneae. Furthermore, even though the tip of the catheter

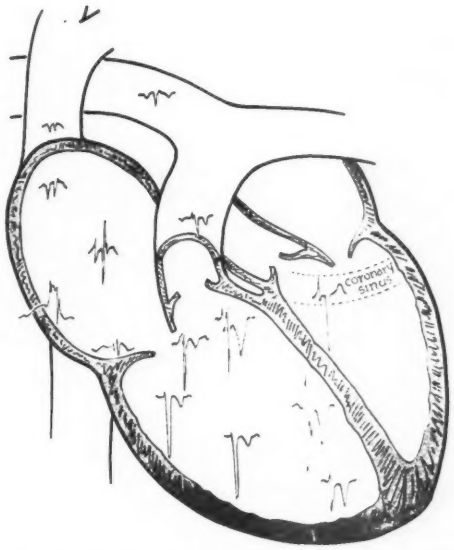

FIG. 1. Composite patterns encountered in usual positions of intracardiac catheter.

is pointed toward the main pulmonary artery when viewed fluoroscopically, it has proven futile to advance the catheter into this vessel once the injury pattern has appeared. Rather it is necessary first to withdraw the tip and then redirect it through a channel which does not elicit such a response. When the catheter is withdrawn from such an "injury area," normal complexes can be expected to reappear within a dozen beats. Since this phenomenon has been recognized and avoided as more than a transient manifestation, catheterization procedures have never been delayed or discontinued because of rhythm disturbances. On the other hand, if these injury currents are ignored, rhythm and conduction disturbances can develop progressively as is demonstrated by an early example in which an intraventricular block developed following the unheeded appearance of an S-T segment elevation (fig. 2*b*).

Additional Information Derived

In addition to the ability to localize the catheter tip within the chambers of the heart

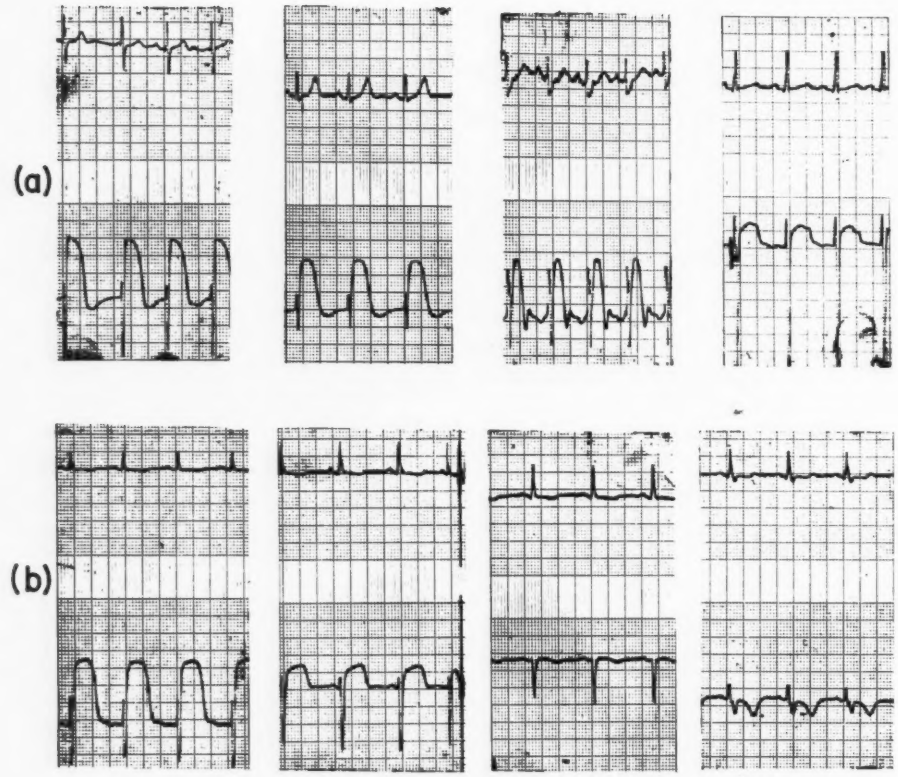

FIG. 2. (*a*) Demonstrates the essential similarity of the injury pattern in widely different underlying states. *Bottom tracing,* intracavity pattern from the right ventricle. Note absence of injury from routine, ordinarily used, lead II monitor tracing above. (*b*) Shows the readiness with which an injury current, not discernible in the usual monitor lead, can evoke bundle-branch block.

electrocardiographically, we have observed additional variants that are diagnostically useful and that do not obscure the basic chamber patterns. Several of the more useful ones are cited.

The intracavity tracing obtained from the left atrium resembles that of the right except that atrial depolarization occurs later. The right atrial P wave is written during the ascending limb of the lead II P wave, whereas the left artial complex is inscribed during the descending limb (fig. 3). This occurrence is useful diagnostically when an abrupt increase in oxygen saturation is detected in the atrium. Ordinarily, such an increase indicates a left-to-right shunt through an atrial septal defect and the atrial pattern will be as expected. It has been our repeated observation that when such occurs in the presence of ostium secundum, the recorded pattern is that of the proximal right atrium. In ostium primum, the abrupt increase in oxygen saturation occurs at a level where the right atrial P wave is diphasic.

It is of additional note that with the catheter tip within the silhouette of a prominent right atrium, abrupt increases in oxygen saturation can occur with 3 less frequent conditions. If the oxygen content becomes that of full saturation, the tip of the catheter may have passed through a functionally

nimportant foramen ovale or into an cutely angled anomalous pulmonary vein. n the latter instance, a right atrial tracing vill be recorded. In the former, the late P vave of the left atrium will be seen. Occaionally, in the presence of peripheral cyaosis, an abrupt increase may occur as well. This may result from the usual left-to-right shunt as with pentalogy. Such an oxygen increase will be equally possible if there is a right-to-left shunt with dilution and resulting partial desaturation of the left atrial blood. In this circumstance, the catheter tip would lie within a small left atrium. The writing of a late P wave in the latter situation easily clarifies this problem, which may be critical when complete anomaly of the pulmonary venous drainage is a diagnostic consideration.

In right atrial enlargement, frequently QRS complexes are obtained from many points within the right atrium that are indistinguishable in configuration from those recorded from within the right ventricle. These complexes begin with initial small R waves followed by deep S waves. Presumably, in right atrial enlargement, the wall of this chamber comes to overlie the right ventricle. During ventricular depolarization, it, too, reflects the QRS of the right ventricle. In such cases it is observed further that the amplitude of the P waves in the right atrium frequently exceeds that of the associated QRS.

Finally, characteristic variants appear to be emerging within the right ventricle that correlate well with a few anatomic lesions. It would seem reasonable to anticipate that such intracavitary patterns, after further and more complete observation, may prove to have considerable diagnostic significance.

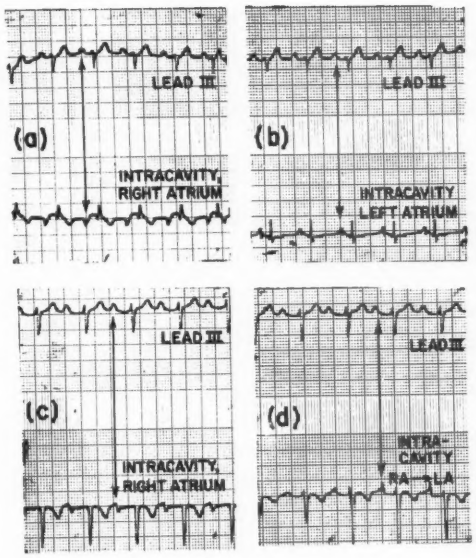

FIG. 3. In the right atrium (*a*) the intracavity P wave corresponds in time to the early part of the P wave in the conventional lead II. In the left atrium of the same patient (*b*) the intracavity P wave occurs distinctly later than the P wave obtained within the right atrium. With the catheter tip in the right atrium of a different patient, record (*c*) was obtained. Subsequently as the tip was advanced into the left atrium, tracing (*d*) was recorded. In both cases an abrupt increase in oxygen saturation was noted within the silhouette of the right atrium.

SUMMARY

The basic characteristic intracardiac tracings obtained at various locations within the right heart in normal individuals have been found to persist as a rule in 150 cases, the majority of which represented congenital heart disease. For this reason it has been possible to reduce greatly the fluoroscopic time required for cardiac catheterization in most cases. The value of recognizing the otherwise inapparent intracardiac current of injury has been discussed. The diagnostic implication of certain contained variants in the endocardial pattern has been presented briefly.

SUMMARIO IN INTERLINGUA

Studios in 150 casos—representante principalmente congenite morbos cardiac— indica que le basic e characteristic curvas intracardiac obtenite a varie sitos intra le corde dextere de subjectos normal se distingue usualmente per lor constantia. In consequentia de iste constatation il ha essite possibile in le majoritate del casos reducer grandemente le tempore fluoroscopic requirite in catheterismo

cardiac. Es discutite le valor de recognoscer le alteremente inapparente currente intracardiac que es determinate per le injurias presente. Le signification diagnostic de certe circumscripte variantes in le comportamento electric del endocardio es brevemente delineate.

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Up to the last 25 years, Cardiology has remained in the hands of physicians with long training at the bedside and the various instrumental methods of investigation devised by Von Basch, Mackenzie, Roentgen, and Einthoven could all be applied by the physician himself directly to his patients, so that the information they provided was incorporated into the clinical picture as a whole and assessed in proper perspective. But today, we are more and more employing instrumental methods which require technical experts to operate them, and which appertain to the Laboratory rather than to the Clinic. Indeed the term "Cardio-vascular Laboratory is already in current use.— Evan Bedford. *Address of the President of the European Society of Cardiology,* IIIrd World Congress of Cardiology, Brussels, September 14-21, 1958, p. 29.

SPECIAL ARTICLE

Problems of Atherosclerosis in Poland

By D. Aleksandrow, M.D. and A. Horst, M.D.

THE increased interest in atherosclerosis in our country dates from 1954 when a coordinating committee for studies of atherosclerosis was created by the Polish Academy of Science. Most of the studies reported in this paper were begun within the last 3 years, many of them initiated and to some extent directly supported by the committee.

Research work on experimental atherosclerosis in laboratory animals carried on in Polish institutes just as in all laboratories of the world is founded on numerous premises concerning the pathogenesis of that disease. Experiments are made on various animals: dogs, chickens, pigeons, rabbits, and rats.

Animal "experimental atherosclerosis" is not a true reflection of atherosclerosis as a disease that has the character of a chronic and progressing process. However, if we create in experimental conditions in a certain limited period of an animal's life the biochemical syndrome of atherosclerosis and produce in the arterial wall the appearance of some fundamental features of the atherosclerotic process in man, we get an opportunity to trace the influence of various factors from the point of view of etiology, pathogenesis, and therapy of atherosclerosis.

In morphologic investigations on the histogenesis of early atherosclerotic changes Rożynek[1] applied subcutaneous injections of allylformate in rabbits fed on a vegetable diet and observed early microscopic changes in the aorta due to a penetration of blood plasma through the damaged endothelium conforming in general to histologic changes in an early necrotic focus of the aorta in man. According to that author the results seem to support the theory of filtration in atherosclerosis.

Damage to the vascular endothelium has been used in our studies of atherosclerotic changes in the aorta of the white rat. We applied Water's[2,3] intravenous injections of allylamine as an endothelial toxic agent, and an egg-yolk emulsion for the purpose of producing hyperlipemia and hypercholesteremia.[4] In these investigations special attention was given to the correlation between the frequency of applying allylamine and the degree of damage of the aorta on the one hand, and the persistence of fat infiltration in its wall, on the other. It was found that microscopic changes consisting in the deposition of fats in the wall of the aorta persisted in these experiments only when the agent injuring the vessels was applied several times and hyperlipemia was produced simultaneously. We may assume that this was a case of superimposition of 2 separate pathologic processes and that the persistence of fatty infiltrations in the arterial wall of the rat depends among others on the degree of injury to the arterial wall.

I should like to mention that we were unable to produce in the rat all the changes that characterize fully developed atherosclerosis in man. Nevertheless, we presented a certain histologic syndrome with some of the fundamental characteristics of the atherosclerotic process, such as imbibition of fatty substances in the intima and media, degenerative and necrotic changes in these sections, and slight proliferative changes in the endothelium or connective tissue (figs. 1 to 6). However, it seems that the structure of the arterial wall in the rat and the resection of these tissues

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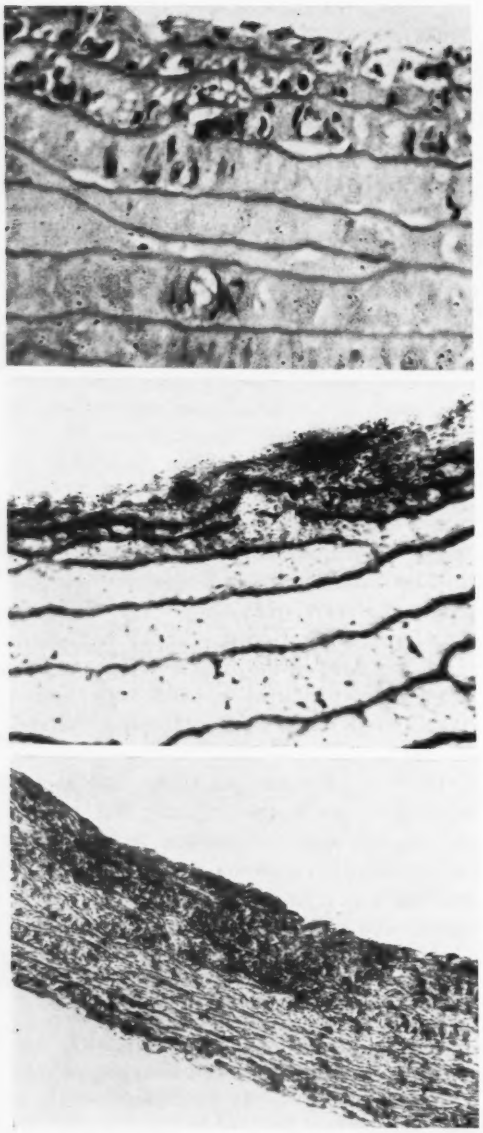

FIG. 1 *Top.* Aorta of rat (arch). Combined allylamine and egg-yolk injury for 6 weeks. Interlamellar edema with necrosis of cells in this region. Reaction of inflammatory type in the upper layers. Hematoxylin and eosin. × 300.

FIG. 2 *Middle.* Same lesion as figure 1. Weigert's elastic stain. Note fragmentation of the upper elastic lamellae. × 300.

FIG. 3 *Bottom.* Aorta of the same rat shown in figures 1 and 2. Diffuse lipid infiltration of the intima and upper medial segments. Sudan III. × 200.

prevent the development of greater and more complicated changes.[5-9]

In general, the white rat as a laboratory test animal of experimental atherosclerosis differs from other animals, especially in a biochemical respect. Our investigations concerning the influence of protamine sulfate on experimental lipemia[11] and comparing the lipemia curve in rats and rabbits after an injection of egg-yolk emulsion and protamine sulfate as an antiheparin agent, showed a distinct difference according to the kind of animal: in rats the high "exogenic" hyperlipemia became compensated on the second day in the group with protamine as well as in that without protamine; in rabbits analogous hyperlipemia decreased more gradually and the administration of protamine delayed the decrease of the level of lipids in blood serum (fig. 7).

In research on experimental atherosclerosis considerable attention is paid to the cholesterol metabolism in the organism. We are aware that without isotopes it will be difficult to solve the problem of its metabolism in atherosclerosis. I shall, however, quote some interesting investigations on the behavior of cholesterol in experimental conditions. Kaleta[12] showed that injections of somatotrophic hormone in dogs raised the level of total cholesterol in the blood up to 45 per cent of the normal values, whereas injections of adrenocorticotrophic hormone caused no change.

In our Institute investigations were made on the influence of emotion on changes of cholesterol in white rats.[13] This subject was studied because of the negative results of investigations on the influence of disturbing factors on the behavior of cholesterol in the blood and because of possible vascular changes in white rats fed on a diet enriched with cholesterol and fat. The animals were irritated by means of an electric stimulant in a special automatic device for a period of 6 weeks. The results of biochemical examinations of irritated rats as compared with control animals allowed us to state that (1) the stimulation had no influence on a rise in the level of cholesterol in blood serum, (2) on the other hand,

TABLE 1.—*Serum Cholesterol of Control and Excited Rats*

Control rats				Excited rats			
	Cholesterol (mg. %)				Cholesterol (mg. %)		
Rat	Total	Free	% Free cholesterol	Rat	Total	Free	% Free cholesterol
1	60	18	30.0	6	72	15	20.8
2	75	20	26.6	7	60	17	28.3
3	87	22	25.4	8	55	13	23.1
4	92	24	26.1	9	60	15	25.0
5	72	19	26.3	10	58	15	25.9
Average	77.2±12.7	20.6±2.38	26.9±1.80	Average	61.0±6.48	15.0±1.41	24.6±2.84

TABLE 2.—*Adrenal Cholesterol of Control and Excited Rats*

Control							Excited						
		Cholesterol (mg. %)			Cholesterol (mg.)				Cholesterol (mg. %)			Cholesterol (mg.)	
Rat	Weight (mg.)	Total	Free	% Free	Total	Free	Rat	Weight (mg.)	Total	Free	% Free	Total	Free
1	39.2	1582	255	16.1	0.62	0.10	6	46.6	1665	450	27.0	0.78	0.21
2	45.05	2044	356	17.4	0.92	0.16	7	64.1	1835	507	27.6	1.18	0.33
3	35.7	2185	420	19.2	0.78	0.15	8	42.7	1932	433	21.9	0.83	0.19
4	38.75	2194	260	11.8	0.85	0.10	9	43.5	2012	597	29.7	0.88	0.26
5	39.0	2372	286	12.0	0.93	0.11	10	54.1	1756	434	24.7	0.95	0.24
Average	39.5	2075	315	15.3	0.82	0.12	Average	50.2	1840	484	26.2	0.92	0.25
	±	±	±	±	±	±		±	±	±	±	±	±
	3.36	299.3	71.0	3.29	0.127	0.029		8.98	138	69.9	2.98	0.156	0.054

TABLE 3.—*Liver Cholesterol of Control and Excited Rats*

Control rats				Excited rats			
	Cholesterol (mg. %)				Cholesterol (mg. %)		
Rat	Total	Free	% Free	Rat	Total	Free	% Free
1	487	373	76.5	6	570	285	50.0
2	573	398	69.4	7	545	272	49.9
3	506	413	81.5	8	600	341	56.3
4	526	421	80.1	9	585	299	52.3
5	526	367	69.4	10	512	277	54.1
Average	524±32.0	394±23.9	75.4±5.76	Average	562±34.7	295±27.8	52.5±2.74

in the group of irritated animals there were distinct changes in free and total cholesterol in the liver and in the suprarenal glands consisting in an increase of the ester content in the liver and a decrease of the esterified form of cholesterol in the suprarenal gland (tables 1-3). These investigations constitute an example of the interest in the hypothesis concerning the role of emotional stimulants in the pathogenesis of atherosclerosis. Investigations in that field are being continued on other animals.

Another factor in the pathogenesis of experimental atherosclerosis is arterial blood pressure. Investigations of Bak et al.[14] on dogs illustrate the influence of hypertension on the dynamics of atherosclerotic changes. The authors made control investigations on the influence of hypertension, hypotension, and normal blood pressure on the course of experimental atherosclerosis by observing arteries of the muscle type in the hind legs of dogs. Hypertension and hypotension in the hind legs were produced by surgical intervention, i.e., by severing the external left hip artery and joining it with the external right hip artery. Thus the blood pressure in the right femoral artery supplied by blood destined for both limbs became elevated approximately by 10 to 30 mm. Hg while it was lowered in the left femoral artery by about 20 to 30 mm. Hg and remained without changes in the arteries of the

FIG. 4 *Top.* Aorta of rat. Combined allylamine and egg-yolk injury for 5 months. Lipid deposits in the deep layers of the media. Sudan black. × 200.

FIG. 5 *Middle.* Combined allylamine and egg-yolk injury for 5 months. Fatty intimal plaque and beginning lipid infiltration of the media. Sudan black. × 200.

FIG. 6 *Bottom.* Aorta of the same rat as in figure 5. Focal thickening of the intima with proliferation of intimal cells. Hematoxylin and eosin. × 200.

forelegs. After the operation the dogs were fed for several months with cholesterol and methylthiouracil. In the arteries of the fore legs no distinct atherosclerotic changes were found. The changes were greatest in the aorta and artery on the side of the anastomosis, i.e. in those arteries in which blood pressure was highest. There were 2 kinds of atherosclerotic changes: lipoid infiltrations, mainly in the media, and atherosclerotic platelets on the internal surface of the intima. The authors draw attention to the importance of the factor of blood pressure which contributed in these experimental conditions to the appearance of atherosclerotic changes in arteries of the muscular type, similar to changes in the aorta.

Baczko[15] examined the influence of estrogens on experimental atherosclerosis in female rabbits that had been previously subjected to total castration and received various doses of estradiol as well as 1/2 Gm. of cholesterol daily dissolved in margarine and mixed with potatoes. The author found no differences in the intensity of atherosclerotic changes in the coronary vessels depending on the dosage of estrogen and as compared with the control group. On the other hand, in the wall of the aorta the changes were the less intense and the less widespread the greater the doses of estradiol given to the animals.

Finally, the problem of treatment of atherosclerosis is the object of many interesting experiments undertaken by Supniewski and Chruściel and their collaborators. In their laboratory the experimental objects were at first chickens of the Leghorn type and at present pigeons for which the authors introduced the method of experimental atherosclerosis obtained by subtotal resection of the thyroid gland and by applying an atherogenic diet consisting of a paste of wheat flour with about 10 per cent (in weight) cholesterol and 25 per cent (in weight) arachid oil.[16] The biochemical and histologic syndrome of atherosclerosis became considerably intensified in birds fed on an atherosclerogenic diet after the removal of the thyroid gland as compared with animals fed on the same diet with intact

hyroid glands. Making use of tests, mainly ith pigeons, of experimental atherosclerosis roduced by the above method or substituting he administration of methylthiouracil for hyroidectomy, these authors investigated the ffect of a number of chemical compounds on he course of vascular and biochemical hanges. I shall describe briefly the particular esults. The anti-atherogenic action of α-phenlpropionic acid in experimental atherosclerosis in chickens[17,18] and pigeons[16,18] was roduced by an acceleration of the lipoid and holesterol metabolism. Investigations on the ffect of disodium-calcium ethylene diamine etraacetate (EDTA) on the course of experimental atherosclerosis in pigeons[19] showed a decrease in the intensity of atherosclerotic changes. Chlorpromazine too diminished and retarded to a considerable extent the development of atherosclerotic changes in experimental atherosclerosis in pigeons.[20] The authors found simultaneously a fall in the level of cholesterol and fatty acids in blood serum as well as electrophoretic changes in sèrum proteins.[21] During an atherogenic diet intramuscular injections of chlorpromazine caused a clearing of hyperlipemic plasma, an inhibition of the increase of albumins, and decrease of α-globulins as well as an increase of β-globulins and β-lipoproteins. M. Chruściel investigated the effect of some simple phosphorus compounds on the course of experimental atherosclerosis in pigeons[22] that received various doses of glycerin sodium phosphate, monopotassium phosphate, and monosodium phosphate. She observed the level of total cholesterol and fatty acids in serum, the behavior of lipoproteids, proteins, and phospholipoproteids as well as the electrocardiographic test of Karp. Phosphates administered parenterally inhibit the development of atherosclerotic changes, confirming the prominent role played by phosphorus compounds in the metabolism of cholesterol and lipids.

Methionine applied by Kleinrock[23,24] at various stages of experimental atherosclerosis affected biochemical changes in the serum of pigeons and distinctly reduced the extent of

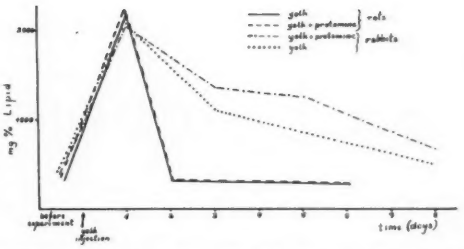

FIG. 7. Effect of egg-yolk injection and protamine administration upon serum lipid level in rats and rabbits.

already macroscopically developed atherosclerotic changes. However, methionine failed to inhibit early changes and had no effect on the picture of microscopic changes. Sodium dehydrocholate, according to the results obtained by Czekaj,[25] also reduced and inhibited already developed atherosclerotic changes in pigeons although it did not prevent their further development. Recently investigations were made in pigeons on the anti-atherogenic action of phenylethylacetic acid (PEAA) which is so typical, not only for the biochemical atherosclerotic syndrome, but also for histologic changes in the arterial wall. Besides, the effect of 2-methyl-2-butano-carboxyl acid on experimental atherosclerosis in pigeons was investigated and it was found that this latter compound inhibits the development of atherosclerotic changes. Of all the anti-atherosclerotic remedies we know 2-methyl-2-butano-carboxyl acid is the most effective.

Para-hydroxypropiophenone belongs to the chemical compounds in which the anti-atherosclerotic effect was not confirmed;[28] Supniewski and co-workers observed the distinct influence of that substance on fat and cholesterol metabolism but they found that it had no effect on atherosclerotic changes in the vessels of pigeons as described in literature[29] in respect to rabbits. 1-Phenylpropanol had not only shown no anti-atherogenic effect but it even increased the deposition of fat substances in the arterial wall in pigeons.[16] In showing the difference in the action of α-phenylpropionic acid, mentioned above, and 1-phenylpropanol as 2 substances chemically closely

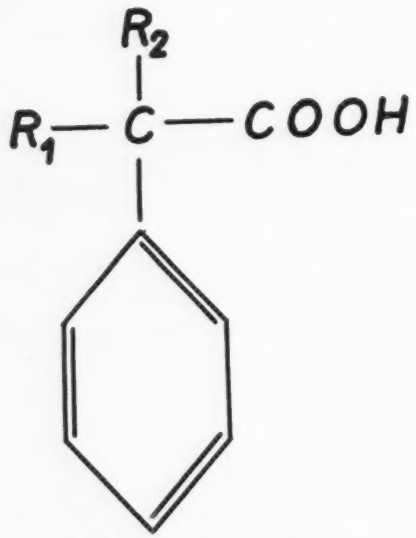

FIG. 8. Structure of necessary group.

related, the authors indicate that for obtaining an anti-atherosclerogenic effect in that group of compounds the presence of the group (fig. 8) is essential. Large doses of calcium glycolate applied in the course of experimental atherosclerosis in pigeons also failed to reduce the intensity of atherosclerotic changes in spite of the hypocholesteremic action and modification of biochemical changes in experimental atherosclerosis.[30]

To studies on the treatment of atherosclerosis belong the recently completed investigations of Samochowiec and associates[31] on the effect of *Cynara scolymus* and *Cynara cardunculus* upon the development of experimental atherosclerosis in white rats. The author applied the test of experimental atherosclerosis according to Hartroft and Thomas,[32] using hydrogenated fat and substituting for thiouracil-neomarkazol (2-carboethoxythio-1-methylglioxaline). The changes in the aorta thus obtained in the form of lipid infiltrations in the endothelium reached in control animals the size of a millet seed. The anti-atherosclerogenic action was particularly effective in the group treated with *Cynara scolymus*. Samochowiec also verified the influence of a commercial preparation of Messrs. Bika containing an extract of *Cynara scolymus*. In this group of experimental animals the author found no anti-atherosclerogenic effect. The investigations he made so far are preliminary to further analyses of the anti-atherosclerogenic properties of various fractions of the vegetable raw material of *Cynara scolymus* and *Cynara cardunculus* and aim at detecting the real active component.

Unfortunately the diagnosis of atherosclerosis in a living subject is still based on the appearance of complications rather than on direct signs of arterial involvement. The early clinical recognition of atherosclerosis arose therefore as one of the chief problems in our clinical investigations. Several Polish medical centers are now dealing with this subject.

In Warsaw some attempts have been made to apply policardiographic methods for the detection of atherosclerotic lesions in great arteries. Chlebus[33] has analyzed carotid arteriograms recorded from normal and coronary subjects by a resonance electrosphygmographic method. The apparatus used in his study was a device of Polish construction.[34] Its chief advantage is the complete elimination of all disturbing effects of the mechanical contact between the receiver and the arterial wall. Figure 9 *Top* shows different patterns of normal arteriograms. Figure 9 *Bottom* shows pathologic tracings from coronary patients. The most characteristic feature of an abnormal tracing is the complete reversion of its plateau, which takes an upright position instead of a downward or horizontal one. In addition, the ascending limb rises more rapidly and the position of the incisura is higher than in normal tracings. Clearly abnormal tracings have been obtained from 80 per cent of the 31 coronary subjects examined. In all subjects nitroglycerin restored temporarily the deformed arteriogram to normal (fig. 10). The aortic pulse wave velocity remained below 7 M. per second in all normal controls and was significantly higher in all coronary subjects.

The arteriograms recorded by the resonance method seem to be of practical value for the diagnosis of atherosclerotic lesions of the great

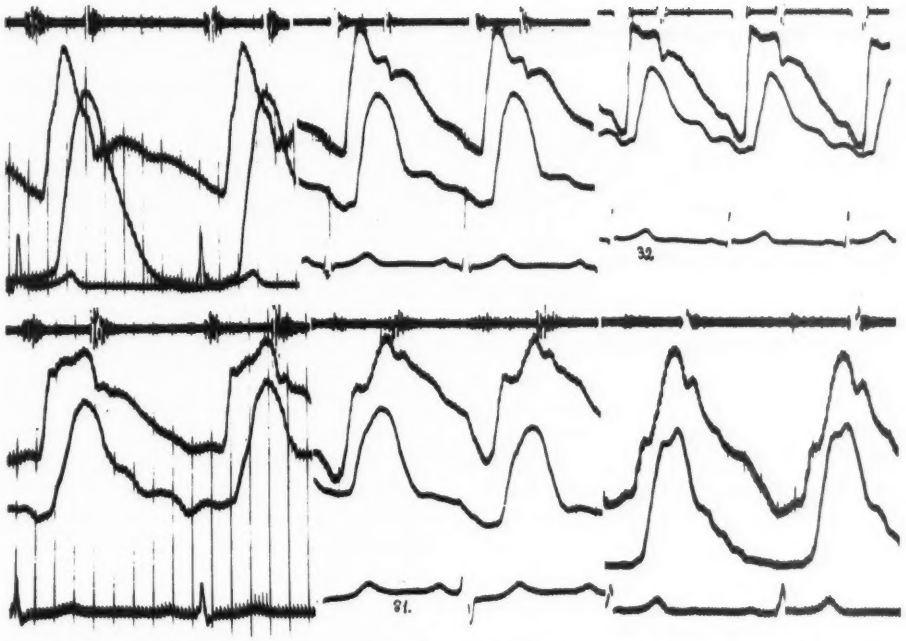

FIG. 9. *Top.* Different patterns of normal arteriograms. From the top: phonocardiogram, arteriogram of the carotid artery, arteriogram of the femoral artery, electrocardiogram II. *Bottom.* Different patterns of pathologic arteriograms.

vessels. A confirmation of this conclusion by a long-term observation of a group of subjects checked by this method is indeed necessary.

In the same study a marked deformation of the ballistocardiogram was found in all coronary patients despite the lack of alterations in the dynamics of their heart beat (the dynamics of the heart beat were estimated according to Blumberger[35] and to Hegglin[36] from simultaneous records of arterial tracings, electrocardiograms, and phonocardiograms). A temporary normalization of the ballistocardiogram occurred after the administration of nitroglycerin. An analysis of the effect of this drug upon the ballistocardiogram, arterial elasticity, and dynamics of the heart beat points to a leading role of arterial elasticity in the determination of ballistocardiographic patterns.

Boreyko-Chodkiewicz and Wotoszczuk[37] published a comparative study of the pulse wave velocity, the air-chamber volume, and its elasticity, calculated according to Wezler and Boger[38] in hypertensive subjects with and without clinical atherosclerotic complications. The observed changes were related to the blood pressure level rather than to the presence or absence of atherosclerotic complications. According to this study the Wezler and Boger method seems to be of dubious value for the detection of atherosclerotic lesions in hypertensive subjects.

In Poznań multiple biochemical, radiologic, and physical tests have been applied simultaneously to a selected group of patients, considered atherosclerotic on clinical grounds.[39] Previous myocardial infarction, hypertensive heart disease, or so-called atherosclerotic heart disease were used as clinical criteria of selection. Electrocardiographic abnormalities were found in all and ballistocardiographic abnormalities in nearly all subjects examined. Fifty-one per cent had an increased heart volume, determined radiologically.[40] Visible cal-

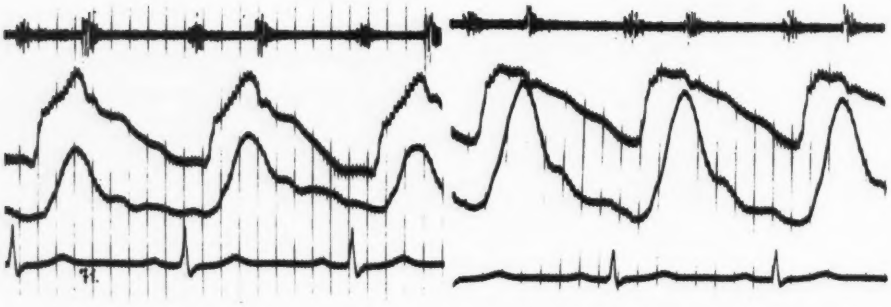

FIG. 10. Pathologic arteriogram of a coronary patient *(Left)* and its normalization after an oral dose of nitroglycerin *(Right)*.

cifications of the pelvic arteries occurred in about 30 per cent, calcifications of the aortic arch were less frequent.[41] The pelvic radiogram is therefore considered a valuable diagnostic aid in doubtful cases. Among the biochemical tests the highest percentage of abnormal results was obtained for the serum lipoprotein patterns, determined electrophoretically, and for the post-heparin clearing test. An abnormal rise of the serum cholesterol level was less frequent; it was found in about 40 per cent of the subjects examined. Most patients had an increased pulse wave velocity and a considerable number showed an abnormal lowering of the skin temperature in the distal parts of the body, suggesting an impaired blood supply.

In a series of reports biochemical features have been compared in patients suffering from atherosclerotic versus inflammatory obliterative arterial disease of the legs. A higher cholesterol serum level[42] and a lower fibrinolytic serum activity[43] was reported in the atherosclerotic group. Both groups differed also in their response to small doses of heparin: the increase of the α-lipoprotein serum level after injection of 3 mg. of heparin was less marked in atherosclerotic subjects.[44] A comparative study of venous blood samples from intact and damaged extremities revealed a marked decrease of the proteolytic activity in venous blood taken from the injured leg. This difference was more constant in atherosclerotic patients than in subjects suffering from thromboangiitis obliterans.[45]

Considerable attention has been given in our country to alimentary lipemia and its modifications after the administration of heparin in normal and atherosclerotic subjects. Both the degree and duration of alimentary lipemia are claimed to be increased in the latter group. This observation has been repeatedly confirmed in our studies, at first by turbidimetric methods[46,48] and recently also by direct chemical determination of glycerol obtained after the hydrolysis of serum neutral fat.[47] Figure 11 shows different courses of alimentary lipemia in normal and atherosclerotic subjects.

The clearing effect of heparin upon alimentary lipemia in vivo as well as the clearing effect in vitro of the patient's plasma taken 15 minutes after heparin injection were compared in normal and coronary subjects.[48,49] Considerably lower values were obtained in coronary subjects. The overlapping of individual values between normal and coronary patients being relatively small, this simple test seems to be of value as an aid to clinical diagnosis. A fair correlation between the results of the post-heparin clearing test and the results of analysis by policardiographic methods could be established in a group of coronary patients examined by both methods.[33]

After the identification of the post-heparin clearing factor as a lipoprotein lipase several reports appeared in the world's medical literature suggesting that this enzymatic system may be responsible for the clearing of alimentary lipemia in normal animals.[50-52]

This suggestion was the starting point for a study by Ciświcka and associates[53] on lipolysis in vivo during the absorption of a fatty meal in normal and atherosclerotic persons. A previous myocardial infarction was accepted as a criterion of atherosclerosis. The intensity of lipolysis was estimated from the increase of unestrified fatty acids concentration in the plasma 3 hours after a standard fatty meal. A marked impairment of lipolysis was found in atherosclerotic subjects. An injection of 5 mg. of heparin at the peak of alimentary lipemia abolished the difference, causing in both groups a marked rise in the serum level of unesterified fatty acids. The results of this study suggest a blocking of normal lipolysis in atherosclerosis. They also suggest that the block may be due to a lack of endogenous heparin. Similar results, indicating a decreased lipolytic activity in atherosclerotic subjects have been obtained also by Szczeklik and co-workers.[54]

The increased blood coagulability may play a role in the pathogenesis of atherosclerotic complications, if not in the pathogenesis of the disease itself. A team of workers from Wroctaw have reported results of a comparative study of the serum lipid patterns and of some coagulation factors in atherosclerotic persons.[55–59]

Patients with coronary disease with or without infarction and patients at various stages of arterial hypertension were selected for this study. A significant rise of the serum cholesterol level and a shortening of the 1-stage prothrombin time, caused chiefly by a rise in the serum content of factor VII, were found in most patients. The alterations were more pronounced in patients with advanced atherosclerosis, myocardial infarction, and late stages of hypertension. In coronary patients, in addition, a lowering of serum fibrinolytic activity was observed. The correlation between serum cholesterol level and observed alterations of blood coagulability was more distinct in coronary than in hypertensive subjects.

The establishment of a relation between fat intake and serum cholesterol level has created

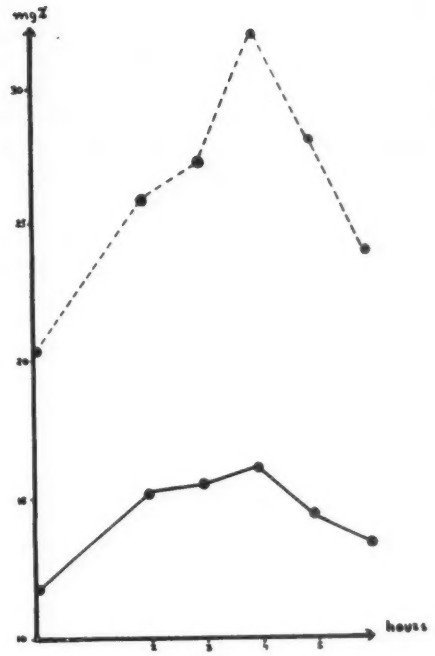

FIG. 11. Serum glycerol level after cream intake. *Solid line*, normal controls (mean values from 15 cases); *dotted line*, atherosclerotic subjects (mean values from 15 cases).

in the past a tendency to reduce fat intake in atherosclerotic subjects. In recent years, with the growing evidence of a hypocholesteremic effect of certain vegetable fats, rich in unsaturated fatty acids, the use of such fats rather than of a low-fat diet has been suggested. An absolute or relative deficiency in unsaturated fatty acids has even been admitted by some authors as a possible cause of metabolic disorders leading to atherosclerosis. In Poland several studies were devoted recently to the problem of unsaturated fatty acids in atherosclerosis. Wiktor and Jacyszyn[60] have reported a significant lowering of the serum level of unsaturated fatty acids in atherosclerotic subjects as compared with normal ones. Ciświcka[61] has followed the serum lipid concentration in coronary subjects receiving for 4 weeks either a low-fat diet or a diet containing daily 100 Gm. of soya-bean oil,

substituted isocalorically for a part of carbohydrates. A marked decrease of the serum cholesterol level occurred in both groups, but it was far more constant in patients receiving soya-bean oil. No statistically significant changes in the serum phospholipids or β-lipoprotein content occurred with either diet within the observation period.

Gajewski[62] compared the effect on blood coagulability of a fatty meal composed chiefly of saturated (cream) or unsaturated (cod liver oil) fatty acids. He observed a shortening of the calcium clotting time, in normal and coronary subjects, and a decrease in serum fibrinolytic activity, in coronary patients only, after intake of cream, but not after intake of cod liver oil.

As part of the investigation on endocrine influences upon lipid metabolism the serum lipid pattern was followed by Sznajderman[63] in 47 women during normal pregnancy. A gradual rise of the serum level of cholesterol, phospholipids, and total lipids was observed during the second and third trimester of pregnancy.

Bruhl[64] has compared the absorption of ingested cholesterol in normal and atherosclerotic subjects. Large individual variations were found in both groups and no statistically significant difference could be established between normal and atherosclerotic persons.

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All knowledge is good. It is impossible to say that any fragment of knowledge, however insignificant or remote from one's ordinary pursuits, may not some day be turned to account. But in medical education, above all things, it is to be recollected that, in order to know a little well, one must be content to be ignorant of a great deal.—Thomas H. Huxley. *American Addresses with a Lecture on the Study of Biology*. London, MacMillan and Co., 1877, p. 113.

CLINICAL PROGRESS

The Resuscitation Problem

By HAMILTON SOUTHWORTH, M.D.

RESUSCITATION is best defined as the restoration of life after apparent death. From prehistoric time death has been considered to be the permanent cessation of breathing, and resuscitation up to 20 or 30 years ago consisted of artificial respiration. Modern medicine, however, has recognized the primacy of the heart beat. Death is now generally determined by cessation of the heart beat, even though it is well known that individual tissues, and even the heart itself, may be capable of full function and therefore of revivification for minutes or hours after legal death. In the dissolution of the total organism it makes little difference whether cardiac arrest or respiratory arrest occurs first; the other is bound to follow rapidly. If both have occurred, the individual is technically dead and resuscitation involves an attempt to restore life, which is different from the physician's usual efforts to preserve life. By the same token, resuscitation should not be regarded as either cardiac or respiratory but as a combined operation best defined by the term cardiorespiratory.

HISTORY

Schiff in 1874[1] first recorded the successful restoration of the heart beat in experimental animals by cardiac massage. Niehaus[1] 5 years later is quoted as the first to attempt massage of the human heart after cardiac arrest, but success was not reported until Starling and Lane in 1902[2] resuscitated by subdiaphragmatic massage an individual who suffered an arrest during an abdominal operation. In 1904 Crile[3] brought back to life a 12-year-old girl whose heart had apparently stopped during brain surgery. An adrenalin solution was perfused into the brachial artery, and when Crile held the bottle high over his head there was a sudden violent shaking of the chest and spurting of blood into the bottle. The operation was finished uneventfully. In 1926 Chevalier Jackson successfully resuscitated a man by cardiac massage who suffered cardiac arrest during gallbladder surgery. Since then in operating rooms all over the world cardiac massage with assisted respiration has been progressively recognized as the basic technic for resuscitation. The first successful defibrillation of the human heart by electric shock seems to have been performed by Beck and his associates in 1947.[4]

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PHYSIOLOGIC BASIS

The term cardiac arrest is generally used to mean the cessation of any effective heart beat. The commonest form is cardiac standstill, in which no ventricular contraction of any type occurs. This may be initiated by sinus arrest with no subsequent idioventricular activity or there may be only ventricular standstill with continuing atrial beats but complete atrioventricular block. Somewhat less common is ventricular fibrillation, in which the rapid and completely disorganized contraction of individual groups of ventricular muscle fibers is totally ineffective in producing any forward movement of the blood. A third type is occasionally seen, in which the heart is found to be beating very feebly but in a coordinated manner without appreciable effect on the circulation.

Regardless of the type of arrest involved, cessation of circulation leads to death of the body's tissues through hypoxia. Most susceptible to oxygen deprivation are the higher centers of the brain, with the adrenal glands, liver, kidneys, and lower brain centers probably following in that order. Numerous experiments on various animals have shown that cessation of brain circulation for more than 5 minutes generally leads to irreparable damage, while restoration of circulation short of this time limit is followed by a high incidence of complete recovery. Individual and species differences exist, but clinical series in man suggest that 3 to 5 minutes, and perhaps the average figure of 4 minutes, represents the critical time limit for restoration of full cerebration. Thus Cole and Corday[5] report that out of 132 cases of attempted human resuscitation, all of the 33 that resulted in complete recovery were initiated within 4 minutes of the arrest. Success, moreover, is directly correlated with the speed with which cardiac massage and proper ventilation are begun.

In both animals and human beings, it is possible at times to reestablish cardiac and respiratory function in the face of serious brain damage. Thus in Cole and Corday's series 44 patients revived only to die days, weeks, or months later in various degrees of decerebration, and 2 survived with apparently permanent cerebral impairment. Happily, most of those individuals who are revived after the safe time limit die within a few days, but the few who linger on and the 1 to 2 per cent who become institutional cases are ample warning of the danger of resuscitation once the critical time limit has passed.

Instances of fully successful human resuscitation have been reported after cardiac arrest of 5 minutes or more and raise the question as to how safe it is to be arbitrary about a 4-minute limit. Most of the earlier cases can be dismissed because the delay was measured as the time from the arrest until the heart began to contract spontaneously rather than from the arrest until massage was commenced. In others the accuracy of the time estimation may be questioned in view of the stress and excitement of the moment. But there probably are real variations. Thus in many an operating-room case there has been hypoxia preceding the actual arrest and brain metabolism may already be impaired. And in those cases in which effective pulmonary ventilation is established an appreciable time before cardiac massage can be started, the safe limit may be slightly longer. Thompson has shown[6] that mechanical methods of ventilation in asphyxiated dogs cause a slow advance of blood through the circulation presumably by means of alternate dilatation and contraction of the pulmonary capillaries. Recently, moreover, some evidence has appeared[7] that individuals resuscitated after 5 to 8 minutes of standstill and with apparent severe brain damage may make complete, recoveries if promptly subjected to hypothermia that is continued for 2 or 3 days. The rationale underlying this maneuver is the theory promoted by Sheldon and co-workers[8] that many of these patients die of cerebral edema rather than of brain-cell necrosis at the time of the initial anoxia. If these results are substantiated, however, the presumption is that the critical time limit will still exist, though it may be lengthened. Whether the incidence of mentally mutilated survivors will be increased or decreased by hypothermia is as yet unknown.

Resuscitation in the Operating Room

The great majority of the reported cases of cardiac resuscitation have occurred in the operating room. In this setting the equipment and the trained personnel for cardiac massage and assisted respiration are at once available. Furthermore, surgical procedures under modern anesthesia provide a not inconsiderable incidence of cardiac arrest. Large hospital series suggest that arrest may occur as often as once in every 2,000 anesthesias[9] and that therefore there may be 5,000 instances each year. The rising incidence up to 1952 seems attributable to the increase both in the complexity and the daring of surgery and in the multiplicity of anesthetic agents and associated medications. Basically, however, the precipitating factors in the susceptible indi-

vidual are generally a combination of hypoxia and vagal stimulation. Especial emphasis has therefore been placed on prevention. As Flagg has stated,[10] "Present emphasis on surgical treatment of cardiac arrest has obscured the fact that cardiac resuscitation is in reality a final desperate supplement to respiratory resuscitation . . . Emphasis should be shifted . . . to the prevention of hypoxia." These statements apply to the situation as generally observed under anesthesia.

Beck has divided the treatment of cardiac arrest into 2 steps: 1. The reestablishment of the oxygen system (the emergency act) by assisted breathing and cardiac massage. 2. The restoration of the spontaneous heart beat. This division is important because it emphasizes the emergency of getting oxygenated blood flowing through the circulation by mechanical means and leaves other considerations, such as defibrillation of the heart, resumption of spontaneous cardiac contractions, and reawakening of the respiratory center, for subsequent consideration. It is beyond the scope of this article to discuss technics in detail, but the essential steps of the emergency act are (1) to reestablish pulmonary ventilation, preferably by intubation and manual breathing using a bag and 100 per cent oxygen and (2) to open the chest and reestablish the blood circulation by cardiac massage. Once the oxygen system has been reestablished, the heart that was in standstill tends to resume its sinus rhythm but may need manual assistance for a period if the contractions are weak. If fibrillation is present or appears during massage, defibrillation is best carried out after a few minutes by electric shock across the ventricles applied by specially designed electrodes and repeated until the fibrillation is broken. Intracardiac injection of drugs is usually of secondary value. Administration of epinephrine (3 to 5 ml. of a 1 to 10,000 solution) strengthens ventricular contraction and may help to initiate spontaneous contraction when the heart in standstill has been massaged for several minutes. In ventricular fibrillation it is useless by itself, as it increases the tendency to fibrillation, but it has been reported as of value after electrical defibrillation in strengthening ventricular contraction. Procaine (3 to 5 ml. of a 1 per cent solution injected into the right ventricle) is indicated in the attempt to terminate ventricular fibrillation if electrical shock seems ineffective.

The emergency of cardiac resuscitation is such that even in the operating room sterile technic is not attempted. While the anesthetist establishes the airway and begins ventilation with 100 per cent oxygen, the surgeon quickly opens the chest, usually by an incision between the fourth and fifth ribs on the left. If the heart is truly in arrest there will be no bleeding. Massage may be carried out with either one hand or two depending on the size of the heart and the surgeon's training. Subsequently, a rib spreader is introduced, and hemostasis as well as sterile technic becomes desirable. Proper surgical closure is not carried out until both heart beat and respirations have proved their ability to continue spontaneously.

In certain surgical patients known to have cardiac disease an increased risk of cardiac arrest during anesthesia can be anticipated. The use of a continuous monitoring electrocardiographic lead during surgery may prove most useful and external electrical stimulation (to be discussed later) is possible in association with it. In hospitals where the surgical staff and operating-room personnel have been well indoctrinated, successful resuscitation in the operating room has been reported in up to 75 per cent of cases.[11] In 1950 under the aegis of the Cleveland Area Heart Society a 2-day postgraduate course in resuscitation was initiated by Beck and Hosler. The influence of the now over 1,500 graduates of this course and of the manual written by Hosler[9] has been felt over the country. Many surgeons have become protagonists for cardiac massage and urge its use outside the operating room.

Resuscitation Outside the Operating Room

In 1950 there appeared the report[12] of a young woman who had developed ventricular fibrillation during cardiac catheterization,

and who survived after thoracotomy, massage, and defibrillation. Since then at least 7 other cases[13] have been published of successful resuscitation in various parts of hospitals distant from the operating room. These often astonishing revivals have led to a school of thought which, in its extreme form, advocates that all internists be equipped with sharp penknives and be trained to perform a thoracotomy on any case that stands a chance of being salvageable. The complications that could result from the overuse of cardiac massage by inadequately trained personnel can easily be imagined. The overenthusiasts fail to recognize the difference in the setup between the operating room and the ward or clinic. In the operating room all needed surgical equipment is at hand, trained surgeons are at work on the patient, an anesthetist is watching his breathing, and arrest should be immediately apparent. Outside the operating and perhaps the recovery room, any or all of these favorable factors may be missing. In addition, the first physician on the scene may well be unfamiliar with the case and also impeded by the presence of family or other patients.

When confronted with an apparent case of sudden exitus not in the operating room, the first duty of the physician is to confirm that cardiac arrest has really occurred. This is best accomplished by deep palpation of the abdomen for aortic pulsations. Time should not be wasted listening for more than a moment for heart sounds or applying a blood pressure cuff but it is most important that syncope and that repetitive attacks of the Stokes-Adams type be differentiated.* Next, the physician should glance rapidly at his watch and record the time. If he feels there is any chance this may be one of the rare medical instances where cardiac resuscitation is indicated, he should then shout for trained assistance, for it is obvious that one person cannot both massage a patient's heart and breathe for him at the same time. At least 2 trained persons must be present from the very start.

A simple technic occasionally effective in resuscitation is pounding on the anterior chest. One good pounding can do little harm but repetitive efforts waste time. Needling of the heart, on the other hand, is generally not to be recommended. It is rarely efficacious (one success out of 40 attempts in Bailey's series[15]) and should only be considered in cases where circumstances make thoracotomy impracticable.

More recently, resuscitation through the use of an external electrical stimulator has been advocated and has achieved some fair success.[16, 17] This is now the method of choice in Stokes-Adams attacks, which tend to be repetitive and where a monitoring electrocardiographic lead can be set up with a warning device when standstill occurs. But external electric stimulation is not as effective in other forms of cardiac standstill as cardiac massage, except perhaps during the first half minute or so of arrest, and wastes invaluable time if thoracotomy subsequently has to be performed. Furthermore, it is totally ineffective in the considerable proportion of cases caused by ventricular fibrillation. To meet this last objection Zoll and associates have devised an external electric defibrillator.[18] The success of this instrument so far has not been great, presumably because it is difficult to defibrillate a heart, even with shocks applied under direct vision to the myocardium itself, until the heart has been "pinked up" with oxygenated blood by massage together with assisted respiration. It is likely that the usefulness of external electrical methods will increase, as technics improve, in severe cardiac patients in whom arrest may be anticipated and who therefore have a pacemaker-defibrillator constantly at their bedside, perhaps with a monitoring lead attached. But at the present time it seems wise to reserve external stimulation and external defibrillation for Stokes-Adams attacks and perhaps

*It has been suggested that, if the physician has an ophthalmoscope with him, a quick look at one fundus may be of value to see if the retinal arteries have become emptied of blood and if beading or segmentation has occurred in the retinal veins.[14] Slow forward movement of blood in the retinal veins can, however, continue for 10 or more minutes after death.

for certain other cases in which cardiac massage seems inadvisable.

Indications for Cardiac Massage Outside the Operating Room

To help the physician, confronted with an instance of cardiac arrest, to decide whether or not to attempt cardiac massage, the following 4 questions have been proposed.[19] It is recommended that he run them rapidly through his mind before making his decision —a process that should take but a few seconds. 1. Has the patient the fundamental health to justify restoration of life? Obviously one would not wish to resuscitate a patient who had a hopeless prognosis. 2. Is it reasonably certain that there is still time to institute massage and that the critical time limit (4 minutes) during which full restoration is still possible has not passed? 3. Has the physician the training, the equipment, and the assistance necessary to undertake both cardiac massage and assisted respiration and to carry them through to a successful conclusion? Here the first emphasis is on the need for at least 2 people who are reasonably trained. The initial equipment need only be a scalpel, for the physician assisting in the breathing can start with mouth-to-mouth respiration. But proper rebreathing apparatus must be available by the time the chest has been opened, and eventually a skilled surgical closure in the operating room is needed. Once massage is under way, and especially if there is resumption of effective cardiac action, there will be brisk bleeding. It is therefore inadvisable to attempt cardiac massage, except under extraordinary circumstances, in a patient's home or in the usual doctor's office outside a hospital. 4. Is the arrest iatrogenic? If the arrest occurs during cardiac catheterization or from an overdose of digitalis, the physician feels a personal responsibility that must affect his actions. Also, he is more liable to a claim of malpractice. It seems generally accepted that the lay press has publicized cardiorespiratory resuscitation to a degree that makes any malpractice claim unlikely against a physician who attempts massage under any reasonable circumstances. There has been one instance of legal action against a physician because he failed to perform a thoracotomy. This case was dismissed by the presiding judge.

At the present time it would seem to be only the rare case occurring outside the operating and recovery rooms that would fulfill the requirements raised by the first 3 questions listed above. Stokes-Adams attacks, as already mentioned, constitute a special category and are best treated by external electrical methods. It is therefore unlikely that the physician, rather than the surgeon, will often be called upon to massage a heart. Certain special situations, however, may present an especial challenge. One of these is the patient with coronary heart disease, either with angina at rest or with a relatively small myocardial infarction, in whom the risk of cardiac arrest is a definite one and where the prognosis otherwise is reasonably good. It has been suggested[10] that such cases may in time be grouped in hospitals in a way to make constant observation possible and a trained physician and nurse immediately available for resuscitation. Endoscopies of various kinds and cardiac catheterizations constitute another special group in which there is increased risk of arrest. Certain intravenous medications, and especially the injection of agents that may be necessary in spite of suspected hypersensitivity, form another group. And further removed from the hospital and the internist, one can list anesthesias in dental offices, drownings at public beaches, and accidental electrocutions at power stations. If cardiorespiratory resuscitation is ever applicable for any of these groups, it must be because special setups have been devised that make it possible to satisfy the special requirements.

Because the occasional case may justify cardiac massage, it is recommended that each internist and general practitioner, as well as each surgeon, think through the problems of cardiorespiratory resuscitation and decide what criteria he believes must first be met. It is also recommended that all physicians be

trained in the simple methods of assisted respiration, and if possible also have the experience of successfully massaging a dog's heart back from standstill. In this way they may be able to help carry through a successful resuscitation, if a case with the proper indications ever comes their way.

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ABSTRACTS

BLOOD COAGULATION AND THROMBOEMBOLISM

Hardaway, R. M., III, and McKay, D. G.: Disseminated Intravascular Coagulation: A Cause of Shock. Ann. Surg. 149: 462 (April), 1959.

The association of shock with disseminated intravascular coagulation has been found in such entities as infantile diarrhea due to *Escherichia coli,* pseudomenbraneous enterocolitis, premature separation of the placenta and eclampsia, amniotic fluid embolization, and incompatible blood transfusion reaction. These experiments were designed to determine the role of intravascular clotting in the production of shock and the effect of heparinization in its prevention. In dogs under pentobarbital anesthesia, catheters were threaded into the aorta through either femoral artery. Through these catheters injections of incompatible blood, amniotic fluid, and heparin were made on one side and arterial pressures determined on the other. In 1 dog pulmonary artery pressure was recorded and in 10 splenic pressures were noted. In 22 dogs, injected with 100 ml. of incompatible blood, there was an average immediate fall of blood pressure of 84.4 mm. Hg. Splenic pressure was elevated in 10 of these. In 1 dog pulmonary artery pressure was measured and found increased. The drop in systemic blood pressure gradually returned to normal over the period of 1 hour. Three dogs died and showed postmortem evidence of thrombosis in pulmonary arteries and capillaries; and in hepatic arterioles and central veins. In the next group of 6 dogs, heparin was initially given followed by incompatible blood. The average fall in blood pressure in this group was 45.5 mm. Hg. In 4 dogs injected amniotic fluid resulted in an average drop of arterial blood pressure of 91.7 mm. Hg. In 4 more dogs, when heparin was given prior to the injection of amniotic fluid, there was only an average drop of 7.3 mm. Hg in systemic pressure. These experiments suggest that the major portion of shock is due to intravascular coagulation. With incompatible blood temporary obstruction of small blood vessels by masses of agglutinated red blood cells seems to be an additional factor. The mechanisms of production of hypotension may be the production of an acute cor pulmonale by obstruction of the pulmonary vascular bed with resultant decrease of return of blood to the left side of the heart and subsequent drop in cardiac output. Decreased venous return as a result of thrombosis of intrahepatic vessels may be another factor. This is supported in these experiments by the finding of rises of splenic vein pressure. It is thought that the transient nature of the shock is due to the dissolution of the thrombi by fibrinolytic enzymes.

LEVINSON

CONGESTIVE HEART FAILURE

Johnson, J. B., Fairley, A., and Carter, C.: Effects of Sublingual Nitroglycerin on Pulmonary Arterial Pressure in Patients with Left Ventricular Failure. Ann. Int. Med. 50: 34 (Jan.), 1959.

The authors have previously reported that the retrosternal distress and breathlessness of paroxysmal dyspnea were frequently relieved by the sublingual administration of nitroglycerin. Further, in patients with hypertensive left ventricular failure, administration of nitroglycerin re-

sulted in a prompt reduction in the associated pulmonary hypertension. The present article is a report of the hemodynamic data obtained by standard right heart catheterization procedures in a group of 13 patients with left heart failure. Seven patients had hypertensive heart disease, 2 had hypertensive and arteriosclerotic heart disease, 3 had heart failure of an undetermined etiology, and 1 had arteriosclerotic heart disease. Mean pulmonary artery pressure was elevated in all patients. In 10 of the 13 patients, a prompt fall (within 30 minutes) in the pulmonary arterial pressure followed the sublingual administration of 0.6 to 1.2 mg. of nitroglycerin. In 4 patients, a wedge-pressure measurement during treatment was obtained, and a reduction in the wedge pressure was also observed. Total pulmonary resistance fell in 12 patients during the first 15 minutes after nitroglycerin therapy. There was no consistent alteration in the cardiac output, nor was there a significant increase in heart rate. The authors suggest that nitroglycerin is an important agent in the management of patients with pulmonary artery hypertension and paroxysmal dyspnea associated with left ventricular failure.

KAYDEN

Petersdorf, R. G., and Merchant, R. K.: A Study of Antibiotic Prophylaxis in Patients with Acute Heart Failure. New England J. Med. **260**: 565 (Mar. 19), 1959.

A study was undertaken to evaluate the suggestion that antibiotics be administered routinely to all patients with acute congestive heart failure, either to prevent the occurrence of pneumonia in a particularly sensitive subject or to treat an infection already present but not clearly defined. A total of 150 patients was investigated with the use of a double-blind technic. Seventy-two randomly selected patients with acute cardiac decompensation were given 2 Gm. of chloramphenicol daily for a week and 78 other patients comparable in age, sex, race, and etiology of the congestive heart failure received placebos. There was no difference in the clinical course of the 2 groups an measured by venous pressure, circulation time, vital capacity, weight loss, and symptomatic improvement. Fever attributable to heart failure per se was present in 42 per cent of the patients and was of greater frequency and longer duration in the controls. In 44 per cent white blood cell counts were elevated above 10,000 on the basis of failure alone and were not affected by antibiotics. Fourteen patients had pneumonia clinically or at autopsy. Eight of these occurred in the antibiotic group and 6 in the control. Of these 14, 4 recovered after penicillin (3 on placebo and 1 on chloramphenicol) but 10 died (3 on placebo and 7 on antibiotic). Prophylaxis with antimicrobials was thus not effective. Review of the x-ray findings indicated that this radiologic examination still remained a relatively accurate method of detecting pneumonia in patients with pulmonary congestion. Other important clues were a purulent sputum, temperature above 101 F. for at least 3 days and a white cell count over 15,000. Adverse reactions to chloramphenicol appeared in 6 patients. The authors concluded that the results did not support the suggestion that antibiotics be given routinely to patients with congestive failure. Instead, they point out that special care should be taken in these patients to discover pulmonary infections early and, once detected, such infections should be vigorously treated with appropriate antimicrobial agents.

SAGALL

CORONARY ARTERY DISEASE

Capeci, N. W., and Levy, R. L.: The Influence of Anticoagulant Therapy on the Incidence of Thromboembolism, Hemorrhage and Cardiac Rupture in Acute Myocardial Infarction. Correlation of Clinical and Autopsy Data in 100 Cases. Am. J. Med. **26**: 76 (Jan.), 1959.

Analysis was made of the clinical records and autopsy protocols of 100 patients with fatal acute myocardial infarction, 50 of whom received adequate anticoagulant therapy. Among the 50 untreated patients, recent cardiac infarction was not recognized ante mortem in 10 instances; in the treated group, 8 diagnoses were not confirmed at autopsy. Mural thrombi were found in 21 of the treated and 22 of the untreated group. Pulmonary emboli were noted at autopsy in 5 of the untreated and 6 of the treated patients. Systemic emboli were found in 6 of the untreated and 9 of the treated cases. All occurred in patients with mural thrombi. Serious hemorrhage outside the heart was found at autopsy in 6 treated cases. In 5 instances, occlusion of the coronary artery was ascribed to hemorrhage beneath an atherosclerotic plaque. Four were in the treated group. Cardiac rupture was found 3 times as often in the group receiving anticoagulants when 239 reported treated patients were compared with 557 untreated.

KURLAND

Epstein, F. H., Block, W. D., Hand, E. A., and Francis, T., Jr.: Familial Hypercholesterolemia, Xanthomatosis and Coronary Heart Disease. Am. J. Med. **26**: 39 (Jan.), 1959.

The mode of inheritance of hypercholesteremia and the relation between abnormal cholesterol metabolism and coronary heart disease are considered in another study of a single family group with familial hypercholesteremia. No clear evidence for any proposed genetic model was obtained. It was suggested that less severe degrees of hypercholesteremia reflect not only a genetic abnormality but the influence of other host on environmental factors. Hypertension was not unduly frequent, and there was no association between blood pressure and cholesterol level. All 6 subjects with xanthomatosis died at an early age. Among the men aged 45 years and over, 17 per cent showed evidence of coronary disease. This high prevalence rate is support for the view that coronary disease is unduly common among these families.

KURLAND

Satinsky, V. P., Kuhn, R., Kompaniez, E. V., and Baum, R. N.: Coronary Curettage. Dis. Chest **35**: 88 (Jan.), 1959.

The development of coronary curettage as a technic in the treatment of severe arteriosclerotic heart disease with intractable angina is reviewed by the authors. A case is presented of a 58-year-old man with a history of posterior myocardial infarction in 1939 and the subsequent development of severe angina treated in 1955 by poudrage, with little relief. Intractable angina recurred, and in 1957 coronary curettage was successfully carried out. Six weeks after the operation the patient had had no recurrence of his angina and his exercise tolerance was markedly increased.

MAXWELL

Day, S. B., and Lillehei, C. W.: Experimental Basis for a New Operation for Coronary Artery Disease. Surgery **45**: 487 (Mar.), 1959.

A right-to-left anatomic shunt was created between the pulmonary artery beyond the semilunar valve and the left atrium in dogs. The fistula was approximately 10 to 12 mm. in length and the shunt approximated 20 per cent of the cardiac output. Two to 4 weeks later the shunt was closed and the circumflex coronary artery was completely occluded. Ninety per cent of the "fistula dogs" survived 1 hour as compared to 28 per cent of normal control dogs. Injection-corrosion casts of the distribution of coronary arteries in the operated dogs demonstrated increased intercoronary channels. Following a shunt procedure, the arterial oxygen saturation was constantly found between 75 and 88 per cent. The present observations indicated that a physiologic vasodilatation of the coronary bed was provoked as a compensatory response to the circulatory changes induced by this degree of hypoxia. In addition there was anatomic proliferation of interarterial and intercoronary anastomoses. This procedure was presented as one for initial application to the large group of patients, selected by means of coronary arteriography, with severe degrees of obstructive coronary arteriosclerosis and not in cardiac decompensation from muscle degeneration. It was also suggested that the slowly obliterative atherosclerotic process in man will be a stimulus to insure that the channels provoked by the operation will remain open, even if the shunt should close or be closed. The presence of these channels should then better prepare the myocardium to withstand a sudden thrombotic episode without muscle death or ventricular fibrillation. In the addendum to this paper the authors report the first human patient undergoing this procedure. The early results were dramatic and sustained to the date of publication.

SHEPS

Weiss, M. M., Sr., and Weiss, M. M., Jr.: Five-Year Follow-Up Study of Men Who Returned to Work after a Myocardial Infarction. J.A.M.A. **168**: 17 (Sept), 1958.

The authors report a 5-year follow-up study of 431 men who returned to some form of gainful employment in an average time of 3 months after their first myocardial infarction. In general such economic rehabilitation paralleled the functional cardiac status. In this group of patients, all occupations were represented but the majority were "white collar" workers. Eighty per cent were below the age of 60. Within 5 years, 33 per cent had ceased to work because of death or retirement. It is of interest that 7 men in their eighth decade returned to gainful employment. Sixty-seven per cent of the 143 patients who ceased work did so because of death. Younger patients worked longer than older ones. It appeared that the complaints of the patient were the best guide toward employment, and no physical finding or test seemed to be prognostic in regard to return to work. No patient who had another infarct or developed failure claimed such was due to his work and hence entitled him to compensation under the Workmen's Com-

pensation Act. The results of this study suggest that the individual who can return but claims he is unable to do so is in need of psychotherapy.

KITCHELL

Morris, J. N., and Crawford, M. D.: Coronary Heart Disease and Physical Activity of Work. Brit. M. J. **2**: 1485 (Dec. 20), 1958.

This report is an attempt to elucidate the relationship of coronary heart disease to the physical activity of work. In this respect 5,000 reports were analyzed from 206 hospitals, on a standard form, of about 25 consecutive unselected necropsies on men between the ages of 45 to 70 years. In general, the results of this survey conform with the data from previous studies that analyzed the problem from slightly different epidemiologic aspects. The general hypothesis was supported in causal terms that the physical activity of work was a protection against coronary heart disease. Men in physically active jobs had less coronary heart disease during middle age, what disease they had was less severe, and they developed it later than men in physically inactive jobs.

KRAUSE

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY AND OTHER GRAPHIC TECHNICS

Effert, S., and Domanig, E.: The Diagnosis of Intra-atrial Tumours and Thrombi by the Ultrasonic Echo Method. German M. Monthly **4**: 1 (Jan.), 1959.

The method of obtaining ultrasonic human echo-cardiograms is described and the value of this technic in identifying intraatrial masses illustrated. The method consisted of transmitting ultrasonic impulses of high frequency (1-2.5 microcycles per second) into the chest in the form of periodic pulses of approximately 10^{-5} seconds in duration at a rate of 200 per second. The sound waves reflected at cardiac and vascular walls were shown as "echograms" on the fluorescent screen of an oscilloscope. A selective echogram of the left atrium could be directing the sound source to the third or fourth left interspace and the relative movements of the left atrium could be depicted electrically or photographically as a curve determined by time and distance. The echograms of the typical patient with mitral stenosis were described and compared with those found in 2 proved cases of intraatrial masses (one patient with a myxoma and the other with a large thrombus).

SAGALL

Ferrero, C., and Gay, E.: Modification of the U Wave in the Rabbit. II: Selective Increase of Right Ventricular Work. Cardiologia **34**: 66, 1959.

Right ventricular work was achieved in the rabbit by compressing the pulmonary artery during systole; the rate was slowed down by simultaneous vagal stimulation. Vagal stimulation by itself was shown not to affect the U wave. In 107 such experiments, U waves appeared in 67 animals, ventricular extrasystole in 45, and positive after potential in 6. Simultaneous recordings of ventricular pressure showed that the distention of the ventricle associated with protodiastolic filling remained practically unchanged. The authors believed that both a mechanical factor (stretching of the myocardial fibers during proto diastole) and an electrical one (change in the supernormal phase of conduction) contributed to the genesis of the U wave.

BRACHFELD

Boyadjian, N., Dechamps, G., and Van Dooren, F.: Ingestion of Massive Doses of Potassium in the Etiologic Diagnosis of Negative T-waves. Acta Cardiol. **13**: 607, 1958.

Alterations of negative T waves following the ingestion of 8 Gm. of potassium chloride were studied. All the negative "coronary" T waves became more negative, whereas negative T waves in a number of other conditions (ventricular hypertrophy, conduction defects, emetine intoxication, myocarditis, and digitalis effect) became less negative or normal. No noticeable side effects followed the ingestion of this dose of potassium.

BRACHFELD

ENDOCARDITIS, MYOCARDITIS, AND PERICARDITIS

Hoffman, F. G., Zimmerman, S. L., Bradley, E. A., and Lapidus, B.: Bacterial Endocarditis after Surgery for Acquired Heart Disease: Report of Two Cases and Review of the Literature. New England J. Med. **260**: 152 (Jan. 22), 1959.

The authors collected 36 cases of bacterial endocarditis occurring after cardiotomy for acquired heart disease and added 2 additional case reports. The clinical aspects of this "new" disease are reviewed. In 23 patients mitral-valve surgery was performed, in 21 patients aortic-val-

vular surgery and in 4 combined aortic and mitral-valve surgery. All of the 21 patients with aortic-valve surgery were males. In 26 patients *Staphylococcus aureus* was the causative agent with 11 coagulase positive and 15 coagulase negative. The incidence of postcardiotomy bacterial endocarditis is estimated to be under 1 per cent. In the patients developing endocarditis within 1 to 4 weeks postoperatively it was felt that the infection was related to a demonstrable extracardiac source. When endocarditis developed in the later postoperative period (after 4 weeks) there was difficulty in demonstrating the source of the organism. In this regard further pathologic study of the healing process of surgically traumatized valves is indicated. The mortality in this group was about 35 per cent, which when corrected for complications of endocarditis was about 27 per cent. No definite correlation existed between valvular calcification and mortality. Review of these cases indicates that the clinical picture of bacterial endocarditis after cardiotomy is atypical and differs from the usual subacute bacterial endocarditis with fever and septicemia as its only consistent findings.

SAGALL

Hughes, A., and Tonks, R. S.: The Role of Micro-Emboli in the Production of Carditis in Hypersensitivity Experiments. J. Path. & Bact. **77**: 207 (Jan.), 1959.

The myocardial lesions produced by injecting platelet clumps into the pulmonary veins of 15 rabbits were compared with those changes produced in rabbits during anaphylaxis and allergic reactions; in addition the blood of the animals subjected to anaphylactic or allergic reactions was carefully examined to determine whether clumping of the blood's formed elements occurred. Small foci of histiocytes and lymphocytes in undamaged myocardium were present in mildly affected hearts, whereas the more severe reactions consisted of true muscle necrosis. Very small platelet clumps produced no lesions, but the larger clumps resulted in varying degrees of cardiac involvement including myocardial necrosis in some instances. Transient clumping of the platelets and other formed elements of the blood occurred in the animals subjected to anaphylaxis and those subjected to allergic reactions. The authors therefore conclude that the cardiac lesions that occur during anaphylaxis or allergic reactions may be produced by entry into the coronary arteries of clumps of platelets or some other of the blood's formed elements.

KARPMAN

Gimlette, T. M. D.: Constrictive Pericarditis. Brit. Heart J. **21**: 9 (Jan.), 1959.

The clinical, radiologic, and electrocardiographic findings in 62 patients with constrictive pericarditis are presented and treatment and results discussed. The etiology and mode of onset had important effects on the final clinical picture and outcome. Seventeen patients were proved to have a tuberculous etiology, and in 39 the etiology was unknown. Forty patients had pericardectomy, and 15 of these were considered cured. In chronic constrictive pericarditis, which usually developed insidiously and often with no evidence of initial acute pericarditis, the results of pericardectomy were much less satisfactory than in acute constriction, which developed rapidly after an attack of pericarditis. In the chronic cases myocardial impairment often predominated over mechanical constrictive effects, as evidenced by cardiac enlargement. The author stresses the importance of early diagnosis, since the sooner pericardectomy is done in acute constrictive pericarditis, the better are the results.

PAUL

HYPERTENSION

Balzer, R., and McCullagh, E. P.: Hypertension in Acromegaly. Am. J. M. Sc. **237**: 449 (April), 1959.

A survey of levels of arterial pressure in 102 patients with acromegaly and 1 with gigantism illustrated an increased incidence of arterial hypertension by the standard of the average diastolic pressure of 100 mm. Hg and also by the age- and sex-adjusted limits of Master et al. By the latter criterion, hypertension was present in 34 per cent of these patients as compared with 10 per cent in a working population. This was somewhat more common in women than in men. No association could be established between hypertension and abnormal carbohydrate metabolism. Thus, acromegaly is not characteristically associated with hypertension, but may contribute to its development in susceptible individuals.

SHEPS

Gillhespy, R. O.: Treatment of Hypertension with "Mio-pressin." Brit. M. J. **1**: 556 (Feb. 28), 1959.

"Mio-pressin" contains the centrally acting agents rauwolfia and protoveratrine together with the long-acting peripheral agent "dibenyline" (5 mg.). This drug was administered to 52 patients with diastolic hypertension both as hospital and out-patients. The out-patient reviews were made

over periods from 1 to 2½ years. Adequate initial observation to observe the lowest blood pressure during rest was used and this level served as the reference point. In the controlled trial, there was a satisfactory fall in diastolic pressure on active treatment and a significant difference between the results of active and inert treatment. Of the 52 patients, 44 maintained or reduced the lowered blood pressure. None had the dose of mio-pressin increased and 26 had the maintenance dose reduced.

KRAUSE

Sjoerdsma, A., Leeper, L. C., Terry, L. L., and Udenfriend, S.: Studies on the Biogenesis and Metabolism of Norepinephrine in Paticnts with Pheochromocytoma. J. Clin. Invest. **38**: 31 (Jan.), 1959.

Chemical studies were performed on tumor tissue, urine, and blood of 7 patients with the diagnosis of pheochromocytoma. C^{14}-labeled dihydroxyphenylalanine and dihydroxyphenylethylanine were used to demonstrate the biogenesis of norepinephrine from these precursors in vitro and in vivo. The 3-methoxy analogue of norepinephrine was found in each of the 4 pheochromocytomas studied. Tissue studies indicated that 2 major metabolites of norepinephrine in man are normetanephrine and 3-methoxy-4-hydroxymandelic acid; the authors suggest that measurement of these substances in the urine may provide valuable information in diagnosing pheochromocytomas. The turnover rate of norepinephrine was found to be very rapid in 3 patients; the tumors of these 3 patients contained only norepinephrine.

KARPMAN

Calesnick, B.: Antihypertensive Action of the Antimicrobial Agent, Furazolidone. Am. J. M. Sc. **236**: 736 (Dec.), 1958.

Furazolidone (Furoxone) is a member of the nitrofuran series of antimicrobial compounds and is used clinically as a topical trichomonacide and as a peroral enteric antibacterial agent. Sixteen patients with uncomplicated primary hypertension were started on a daily peroral dosage of 200 mg. 4 times a day. This was reduced gradually when the hypotensive response became stabilized. In this group the reduction in arterial blood pressure occurred between the second and eighth weeks with no subjective or objective evidence of orthostatic hypertension. The main side effect was nausea but this disappeared after 2 to 4 weeks of continuous treatment. Normocytic anemia was detected in several Negro patients but was not seen in Caucasian subjects. There was also a brownish discoloration of the urine due to the presence of a small amount of the drug and its metabolites. One patient developed an acute disulfiram type of reaction to beer while on the drug. The blood pressure in normotensive individuals was unaltered by furazolidone. There were no changes in the intestinal flora, blood volume, protein-bound iodine and electrocardiogram in the patients studied. There was a decrease in total exchangeable sodium space and an increase in renal excretion of sodium without alteration of serum sodium and potassium. The classical disulfiram action in 1 subject in addition to the in vitro evidence of interruption in various metabolic pathways of carbohydrate metabolism suggests to the author that the hypotensive action of furazolidone may be based on these effects.

SHEPS

PATHOLOGY

Wynn, W. A., and Montgomery, G. L.: Chemical Injury of Arteries. J. Path. & Bact. **77**: 63 (Jan.), 1959.

A variety of chemical substances in aqueous solution were injected into isolated segments of the rabbit femoral artery and allowed to remain in place for 2 minutes before being withdrawn. These test substances damaged not only the endothelium but also the arterial wall itself. Intravascular thrombosis was not a constant finding and, when it occurred, was usually delayed for at least 72 hours. Slowing of the blood stream in the damaged arterial segments increased the incidence of thrombosis. Intimal thickenings with or without fibrin deposits were observed in the damaged arterial segments; these changes were similar to those seen in traumatic, inflammatory, or neoplastic vascular lesions.

KARPMAN

Farulla, A., Bompiani, G. D., and Naro, G.: The Internal Layers of the Right Ventricle in Chronic Cardio-Respiratory Insufficiency. Acta cardiol. **13**: 571, 1958.

The subendocardial layers of the right ventricle were studied in subjects who had died from chronic cardiorespiratory insufficiency. The morphologic picture was characterized by structural alterations of the wall of the "vena minima cordis," perivascular edema, and the presence of zones in which the diffuse interfascicular edema was reminiscent of the histologic picture described by Banti as "venous cirrhosis of the heart." These findings suggest that the lesion originates in the alteration of the deep venous return, which

underlines the specific effect that the thebesian system exerts on the right ventricular subendocardium. However, the role of arterial ischemia resulting from compression of the subendocardial arterial plexus secondary to elevated pressure in the right ventricle should also be considered.

BRACHFELD

PHARMACOLOGY

Baker, J. E., Leidy, H. L., Brooks, A. V., and Beyer, K. H.: The Physiological Disposition of Chlorothiazide (Diuril) in the Dog. J. Pharmacol. & Exper. Therap. **126**: 295 (April), 1959.

The distribution and fate of chlorothiazide in the dog are described. Labeled chlorothiazide was prepared using C^{14} formic acid in the procedure. An analytic technic for the determination of chlorothiazide in biological fluids is given. Chlorothiazide is excreted rapidly and completely in the urine following its intravenous administration to dogs. Renal clearance studies show that chlorothiazide is excreted by the renal tubules; the tubular secretory component can be inhibited by probenecid. In the nephrectomized dogs, plasma levels of a single intravenous dose of chlorothiazide fall as a result of rapid elimination in the bile, as much as 41 per cent of a dose being excreted in the bile in 4 hours. Some 30 to 60 per cent of a single oral dose of chlorothiazide is excreted in the urine. No accumulation of drug could be demonstrated in erythrocytes or tissues following C^{14}-labeled chlorothiazide.

RINZLER

Farah, A., Bender, C. H., Kruse, R., and Cafruny, E.: The Influence of Acidosis and Alkalosis on Mercurial-Induced Diuresis and Sulfhydryl Changes in the Kidney. J. Pharmacol. & Exper. Therap. **126**: 309 (April), 1959.

Changes in acid-base balance influenced an organic mercurial-induced diuresis. It was further shown that diuretic doses of mersalyl caused a reduction of protein-bound sulfhydryl concentration in specific kidney cells. This study correlated mercury-induced diuresis during acidosis and alkalosis with renal sulfhydryl changes in rats and dogs. In dogs alkalosis decreased mersalyl-induced sulfhydryl changes and diuresis when compared with acidotic animals. Changes in acid-base balance did not influence mercury bichloride-induced renal cellular sulfhydryl changes in the terminal part of the proximal tubule although alkalosis depressed mercury bichloride-induced diuresis as compared to acidotic dogs. The results were compatible with the interpretation that with the organic mercurial diuretics a splitting of the carbon-mercury bond may be operative; however, other factors such as electrolyte load are also important in determining the extent of a mercurial diuresis.

RINZLER

Chaudri, K.: Renal Effects of Veratridine. Brit. J. Pharmacol. **14**: 74 (Mar.), 1959.

Veratridine hydrochloride given subcutaneously inhibited water diuresis in unanesthetized rats, and this effect was more pronounced during urethane anesthesia. When given intravenously, antidiuresis was even more pronounced and was accompanied by marked hypotension. Pretreatment with atropine did not affect the hypotension but reduced or abolished the antidiuretic effect. During osmotic diuresis, veratridine had its usual antidiuretic action. Urine excreted during veratridine-induced antidiuresis had an antidiuretic action in other animals, and this action was not affected by treatment of the urine with thioglycollate. Small amounts of a veratridine-like substance were found in the urine during veratridine-induced diuresis. These results were thought to indicate that the renal action of veratridine was not mediated by the neurohypophysis.

ROGERS

Strausak, A., Cottier, P., and Schmid, A.: Ethyl, 7-hydroxyaceto flavone (Recordil) in the Treatment of Angina Pectoris. Effect on Hemodynamics and on Renal Function. Cardiologia **34**: 138, 1959.

The effect of Recordil, 15 to 30 mg. given 3 times daily, was investigated in 20 patients with angina pectoris and compared with that of a placebo. In 85 per cent of the patients anginal pain disappeared or became less severe, and exercise tolerance improved. Of the 15 patients investigated electrocardiographically, the records showed unquestionable improvement in 3, no change in 11, and deterioration in 1. The water-soluble form of this preparation, given intravenously in doses of 30 mg., had no immediate effect on blood pressure, pulse rate, or cardiac output; the effect on renal function was variable.

BRACHFELD

Preziosi, P., Bianchi, A., Loscalzo, B., and De Schaep-Dryver, A. F.: On the Pharmacology of Chlorothiazide—with Special Regard to Its Diuretic and Anti-hypertensive Effects. Arch. int. pharmacodyn. **118**: 467 (Feb.), 1959.

Chlorothiazide was found to have no effect on the isolated guinea pig and rabbit hearts in doses

below 250 μg.; higher doses had only an occasional, slight and transient negative chronotropic effect. This effect could be observed with lower doses in exhausted hearts. The effects of epinephrine and norepinephrine on the isolated heart were not altered. In high doses (66 mg. per Kg.) a slightly delayed lowering of arterial pressure was noted in dogs. A decrease of the vasopressor responses to epinephrine, norepinephrine and hypertensine was found to be maximal about 30 minutes after administration of chlorothiazide and lasted 60 to 150 minutes. The drug did not produce any effect on topical application to the carotid sinus areas and did not inhibit the topical action of epinephrine and norepinephrine on these areas. Chlorothiazide had no effect on neurogenic hypertension in dogs, even at high doses. The depressant action on the peripheral vascular smooth muscle, which chlorothiazide was found to have, may explain the antihypertensive effects of this substance as well as its potentiating action upon the antihypertensive effects of various drugs.

BRACHFELD

Dresel, P. E., and Nickerson, M.: The Role of Potassium in Epinephrine-Induced Cardiac Arrhythmias. J. Pharmacol. & Exper. Therap. **125**: 142 (Feb.), 1959.

The authors have investigated the possible causal relationship between an induced hyperkalemia and an epinephrine-induced ventricular arrhythmia in pentobarbital anesthetized dogs. The rise in blood potassium after epinephrine administration was not quantitatively correlated with the induction of arrhythmias, although the level obtained was on the borderline of being sufficient to induce arrhythmia had it occurred at the time of maximum epinephrine concentration. Combined injection of subthreshold doses of epinephrine and exogenous potassium did not produce an arrhythmia unless the plasma levels attained were considerably above those occurring after an arrhythmia-inducing dose of epinephrine. The ability of isoproterenol to induce cardiac arrhythmias was not enhanced by the infusion of potassium to produce blood levels comparable to those resulting from an arrhythmia-inducing dose of epinephrine. The exclusion of the liver from the circulation and its subsequent abolition of the epinephrine-induced hyperkalemia did not prevent the production of arrhythmias by epinephrine. Very high levels of plasma potassium whether endogenous or exogenous in origin may facilitate the production of arrhythmias. From these observations it was concluded that no causal relationship existed between hyperkalemia and arrhythmia-inducing actions of epinephrine.

RINZLER

Burn, J. H., and Rand, M. J.: Fall of Blood Pressure after a Noradrenaline Infusion and Its Treatment by Pressor Agents. Brit. M. J. **1**: 394 (Feb. 14), 1959.

When animals were injected with reserpine the store of norepinephrine disappeared. When norepinephrine was infused at a constant rate into spinal cats, the blood pressure rose steeply at first and then fell. This was particularly evident when such cats had been previously treated with reserpine. When an intravenous drip of norepinephrine had been given and the blood pressure fell to a low level on omitting the drug, the blood vessels became increasingly insensitive to its pressor effect. This low sensitivity appeared to be due to storage of the norepinephrine in the wall of the blood vessels. At this point sympathetic tone seemed to be absent but was apparently restored by the injection of a pressor amine such as ephedrine, which promptly raised the blood pressure. Therefore, under these circumstances, the correct procedure was to use one of the pressor amines rather than to resume the drip of norepinephrine.

KRAUSE

PHYSIOLOGY

Farrand, R. L., and Horvath, S. M.: Effects of Khellin on Coronary Blood Flow and Related Metabolic Functions. Am. J. Physiol. **196**: 391 (Feb.), 1959.

The effects of khellin upon the cardiovascular system of the dog were measured in 10 anesthetized animals. Coronary blood flow and cardiac output samples were drawn during the control period and at 10, 40, and 80 minutes after the intravenous administration of 1 mg. per Kg. body weight of khellin. Cardiac output was calculated by the direct Fick principle and coronary blood flow by the nitrous oxide method. There was a significant increase in the arterial oxygen content at the 10- and 40-minute interval but no change was observed at 80 minutes. An increase in arterial-mixed venous oxygen difference occurred at 40 and 80 minutes. No change in systemic arterial pressure or cardiac output was noted at any time. Coronary blood flow had decreased slightly at 80 minutes. Any possible beneficial effect of khellin would have to be ascribed to an altered metabolism of the myocardial tissues rather than to coronary vasodilatation.

KAYDEN

Mithoefer, J. C.: Inhibition of Carbonic Anhydrase: Its Effect on Carbon Dioxide Elimination by the Lungs. J. Appl. Physiol. **14**: 109 (Jan.), 1959.

An immediate fall in carbon dioxide output relative to the ventilation occurs when carbonic anhydrase is inhibited and this results in carbon dioxide retention until a new steady state has been reached. This was studied in dogs by measuring the effect of hyperventilation on carbon dioxide stores during carbonic anhydrase inhibition, by measuring alveolar gas tensions when ventilation was constant and when the ventilation was suddenly artificially changed to a new level, and by measuring carbon dioxide output directly.

RINZLER

PULMONARY DISEASES

Robin, E. D., Julian, D. G., Travis, D. M., and Crump, C. H.: A Physiologic Approach to the Diagnosis of Acute Pulmonary Embolism. New England J. Med. **260**: 586 (Mar.), 1959.

Simultaneous measurements of arterial and end-tidal carbon dioxide tensions were reported for 24 normal subjects and 11 patients with a suspected diagnosis of pulmonary vascular obstruction. In the normal subject the peak end-tidal carbon dioxide tension represented alveolar carbon dioxide tension and was essentially equal to the arterial carbon dioxide tension. In the absence of pulmonary infarction a difference of less than 5 mm. Hg in the measurements were found to indicate either no pulmonary embolism or as embolus occluding less than the equivalent of a lobar branch of a pulmonary artery. A large difference was found, in the absence of pulmonary emphysema, to indicate a pulmonary vascular occlusion. The limitations of this technic and its clinical value in the diagnosis of suspected pulmonary embolism or thrombosis were discussed.

SAGALL

Boake, W. C., Daley, R., and McMillan, I. K. R.: Observations on Hypoxic Pulmonary Hypertension. Brit. Heart J. **21**: 31 (Jan.), 1959.

Observations were made on the mechanism of hypoxic pulmonary hypertension in order to localize the sites that are sensitive to oxygen lack. The investigations were carried out in the intact dog, by an extracorporeal circulation arrangement to maintain the pulmonary artery saturation at near normal levels while the oxygen concentration in the inspired air was lowered. The rise in pulmonary artery pressure occurring during hypoxia could be reduced by perfusing the pulmonary artery with well-oxygenated blood. These experiments suggest that the mechanism causing pulmonary hypertension in the hypoxic dog was elicited by impulses from receptors in the pulmonary capillaries as well as from receptors in the air passages.

PAUL

ROENTGENOLOGY

Kalinowski, G., Lichterfeld, A., and Spengler F.: Roentgenological Method for the Evaluation of the Severity of Pulmonary Emphysema. Fortschr. Roentgenstr. **90**: 53 (Jan.), 1959.

In 109 patients sagittal roentgenograms were made in extreme inspiration and expiration at 72-75 kV and 80-90 mAh; films from the same package were used and developed synchronously. In persons without emphysema (grade 0) the diaphragm, heart, or vertebral column could not be recognized definitely in maximal expiration; in grade 1 emphysema these features could be just recognized; in grade II emphysema they could be well differentiated, while in grade III emphysema the difference in the translucency of the retrocardiac and retrosternal spaces in maximal expiration and inspiration was only slight. In all patients the residual pulmonary space was determined by the nitrogen method and expressed as a percentage of the total vital capacity. In normal persons (grade 0) this percentage was less than 30, in grade I it was 30 to 40, in grade II 40 to 50, and in grade III more than 50. The grades of emphysema measured according to the roentgenologic and spirographic methods showed complete agreement in 84 per cent of the patients; in 15 per cent the discrepancy was 1 grade, and in 1.8 it was 2 grades.

LEPESCHKIN

Thal, A. P., Richards, L. S., Greenspan, R., and Murray, M. J.: Arteriographic Studies of the Coronary Arteries in Ischemic Heart Disease. J.A.M.A. **168**: 2104 (Dec. 20), 1959.

The coronary arteries can be visualized in unanesthetized patients by injecting a radiopaque medium through a catheter into the ascending aorta. After positioning the tip of the catheter about 2.5 cm. above the aortic valve, special technics are used to predetermine the phase and duration of the injection whereby 40 to 50 ml. of radiopaque medium is injected in 0.6 to 0.8 seconds. Subsequent film exposures must be properly timed. This type of study allows for critical analysis of the coronary arterial system in patients with severe coronary sclerosis. Myocardial ische-

ia can frequently be diagnosed with great accuey by means of history and electrocardiographic ndings but there remains a small group of atients in whom the diagnosis remains in doubt spite of careful clinical study. These doubts an be resolved by coronary arteriography. In 4 epresentative patients reported by the authors, 2 riginally referred for surgical treatment, were hown to have normal coronary vessels. The most lefinitive roentgenologic sign of coronary artery lisease is complete or partial occlusion of the najor vessel.

KITCHELL

SURGERY, AND CARDIOVASCULAR DISEASE

Lobpreis, E. L.: The Danger of Hypoglycemia during Cardiopulmonary Bypass. J. Thoracic Surg. **37**: 334 (Mar.), 1959.

Hypoglycemia must be added as one of the many pitfalls that beset the use of an extracorporeal circulation. Studies were made of 4-hour-old and 18-hour-old heparinized blood. In the first group a glucose determination by the Somogyi-Nelson method was done shortly after drawing the blood and then another determination after keeping the blood at 37° C. up to about 3 hours. There was a calculated glucose consumption of 10.59 ± 0.31 mg. This blood was mixed and used for the bypass procedure. The glucose level of blood in the oxygenator 20 minutes before starting the procedure was 44.2 mg. per cent, the patient's arterial blood level was 125.2 mg. per cent. In the second series the samples were drawn about 18 hours before the procedure. The bottles were kept cool for about 4 hours when the first sample was drawn and then kept in the refrigerator over night. The second glucose determination was then made. The bottles were then placed in a warm-water bath and the third glucose determination was obtained 50 minutes before the bypass procedure. In this last test the blood sugar had dropped to an average of 25.59 mg. per cent for 12 bottles. If glucose had not been added, a blood glucose level of about 16.77 mg. per cent could have been reached by the beginning of the bypass procedure. Since deficiency of blood glucose is tantamount to anoxia for the brain, the importance of maintenance of the glucose level is seen. A sudden drop in glucose concentration may be as hazardous as the low level itself. It is suggested that the addition of 1 ml. of 50 per cent glucose solution (500 mg.) to each bottle of blood would avoid the dangers of hypoglycemia. The ABBO-Vac bottle uses 18 mg. of heparin in 30 ml. of normal saline for 470 ml. of blood. When the above amount of glucose is added it should allow for 70 more hours of refrigeration and 10 more hours of incubation. It has been shown that the decline in anticoagulant action of heparin before and after addition of blood in saline glucose solutions is not different from that in normal saline in the first 24 hours and in the concentration of glucose suggested. The addition of these small increments of glucose would not increase the hazards of hemolysis.

LEVINSON

VALVULAR HEART DISEASE

Holmgren, A., Jonsson, B., Linderholm, H., Sjöstrand, T., and Ström, G.: Physical Working Capacity in Cases of Mitral Valvular Disease in Relation to Heart Volume, Total Amount of Hemoglobin and Stroke Volume. Acta med. scandinav. **162**: 99, 1958.

The need of an objective evaluation of functional incapacity in patients with mitral valvular disease preoperatively has led the authors to investigate the physical working capacity by means of a bicycle ergometer, and in this report they correlated various hemodynamic values determined by cardiac catheterization, calculated total amount of hemoglobin, and heart volume with the physical working capacity in a group of 42 patients with mitral valvular disease. In normal subjects the working capacity was limited by the oxygen transport capacity (also expressed as the oxygen consumption per heart beat or oxygen pulse) and a close correlation was found between the working capacity at a given pulse rate and either the total amount of hemoglobin or the heart volume. The physical working capacity was decreased in the patients with predominant mitral stenosis when compared to normal standards; this deviation was more marked if the capacity was related to the total hemoglobin value, which was within the normal range, or to the heart volume, which was increased in the majority of patients. In mitral stenosis the authors believe that the working capacity is decreased on the basis of a small stroke volume with decreased maximal cardiac output. The degree of hemodynamic disturbance measured during cardiac catheterization was also found to be correlated with the degree of reduction in physical working capacity as measured by the ergometer. Patients with mitral insufficiency showed increased heart volumes although the pulmonary resistance and the working capacity in relation to the total amount of hemoglobin were normal.

FREEDBERG

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.
Telephone Gramercy 7-9170

ASSOCIATION PRESENTS AWARDS AT SCIENTIFIC SESSIONS

Among the honors conferred on physicians for outstanding service in advancing the heart program and for achievement in cardiovascular research by the American Heart Association at its Scientific Sessions, were the following:

Gold Heart Awards

The Gold Heart Awards were presented at the Annual Dinner to Edgar V. Allen, M.D., past-President of the American Heart Association and Senior Consultant in Medicine at the Mayo Clinic; David D. Rutstein, M.D., Professor of Preventive Medicine, Harvard Medical School; and Samuel A. Levine, M.D., Clinical Professor of Medicine, Harvard Medical School.

Dr. Allen and Dr. Rutstein were cited for their contributions in advancing the objectives and program of the Association. Dr. Levine was honored for his outstanding achievements in clinical cardiology.

Lasker Award

Robert E. Gross, M.D., Professor of Children's Surgery, Harvard Medical School, received the Albert Lasker Award of the American Heart Association for distinguished achievement in the field of cardiovascular research and especially for his pioneering experimental work in the field of cardiovascular surgery. The award consists of a statuette of the *Winged Victory of Samothrace* and an honorarium of $2,500.

FILMS ON STROKE MANAGEMENT ISSUED BY ASSOCIATION

A professional film on strokes of interest to the general practitioner has been issued by the American Heart Association. The film, "Cerebral Vascular Diseases—The Challenge of Management," shows technics for recovery and rehabilitation through use of services and equipment available to every physician with a stroke patient. It stresses the need for early and continued care and for cooperation of the patient and his family throughout the recovery period.

Many affiliates and chapters of the Association are planning showings of the film to physician audiences in connection with scientific programs on the problem of rehabilitating stroke patients.

"Second Chance," a lay film based on the same case history, has also been produced for the Association and its affiliates. It can be of help to physicians in instructing families of victims on rehabilitation procedures and as a visual aid in addressing non-professional groups.

Both are 16mm. black-and-white films, produced and directed by George C. Stoney and Associates for the American Heart Association. "Second Chance" is available to physicians on loan from local Heart Associations or from the American Heart Association, 44 East 23rd Street, New York 10, N. Y.

A second professional film on strokes, "Cerebral Vascular Diseases—The Challenge of

Diagnosis," is in preparation for early release by the Heart Association.

MEETINGS CALENDAR

November 8-9: American Heart Association's Council on Arteriosclerosis, Chicago. Aaron Kellner, New York Hospital, 525 E. 68th Street, New York 21, N. Y.

November 9-13: American College of Chest Physicians Annual Course on Diseases of the Chest, New York. Murray Kornfeld, 112 E. Chestnut Street, Chicago 11, Illinois.

November 10-12: Conference on Electrical Techniques in Medicine and Biology, Philadelphia. Herman P. Schwan, University of Pennsylvania, Philadelphia, Pa.

November 12-13: International Symposium on Cardiology in Aviation, Texas. Lawrence E. Lamb, Department of Internal Medicine, School of Aviation Medicine, USAF, Brooks Air Force Base, Texas.

November 13-14: Annual Symposium on Cinefluorography, Rochester. George H. Ramsey, Department of Radiology, Strong Memorial Hospital, Rochester 20, N. Y.

November 29-30: American College of Chest Physicians, Dallas. Murray Kornfeld, 112 E. Chestnut Street, Chicago 11, Ill.

December 7-11: American College of Chest Physicians Annual Course on Diseases of the Chest, Los Angeles. Murray Kornfeld, 112 E. Chestnut Street, Chicago 11, Ill.

1960

February 3-6: American College of Radiology, New Orleans. William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill.

February 18-20: Central Surgical Association, Chicago. Angus D. McLachlin, Victoria Hospital, London, Ontario, Canada.

March 19-24: American Academy of General Practice, Philadelphia. Mac F. Cahal, Volker Blvd. at Brookside, Kansas City 12, Mo.

March 21-24: Southeastern Surgical Congress, New Orleans. B. T. Beasley, 1032 Hurt Bldg., Atlanta 3, Ga.

March 26-27: American Psychosomatic Society, Montreal. Eric Wittkower, 265 Nassau Road, Roosevelt, N.Y.

March 28-31: Southwestern Surgical Congress, Las Vegas. Mary O'Leary, 1213 Medical Arts Building, Oklahoma City, Okla.

April 1-3: American Society of Internal Medicine, San Francisco. R. L. Richards, 350 Post Street, San Francisco 8, Calif.

April 3-6: American Surgical Association, White Sulphur Springs, W. Va. W. A. Altemeier, Cincinnati General Hospital, Cincinnati 29, Ohio.

April 4-9: American College of Physicians, San Francisco. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

ABROAD

1960

May 2-11: Pan American Medical Association Congress, Mexico City. Joseph J. Eller, 745 Fifth Avenue, New York 22, N. Y.

May 6-8: International Congress of Phlebology, Chambery, France. J. Marmasse, 3 Rue de la Republique, Orleans, Loiret, France.

May 15-18: International College of Surgeons, International Congress, Rome. Secretariat, 1516 Lake Shore Drive, Chicago 10, Ill.

May 23-28: Asian-Pacific Congress of Cardiology, Melbourne, Australia. A. E. Doyle, Alfred Hospital, Melbourne S. 1, Victoria, Australia.

August 14-20: Inter-American Congress of Cardiology, Rio de Janeiro. Secretariat, P. Box 1594, Rio de Janeiro, Brazil.

August 28-September 1: International Congress on Diseases of the Chest, Vienna. A. Sattler, American College of Chest Physicians, Frankgasse 8, Vienna, Austria.

September 1-3: First International Congress of Nephrology, Geneva. G. Richet, 149 Rue de Sevres, Paris 15, France.

September 18-25: European Congress of Cardiology, Rome. Secretariat, Clinica Medica, University of Rome, Italy.

THE COUNCIL ON ARTERIOSCLEROSIS OF THE AMERICAN HEART ASSOCIATION
THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

PROGRAM AND PROCEEDINGS OF THE THIRTEENTH ANNUAL MEETING AT THE KNICKERBOCKER HOTEL, CHICAGO, ILLINOIS NOVEMBER 8 AND 9, 1959

(All papers except the Addresses will be limited to 10 minutes for presentation plus 5 minutes for discussion.)

SUNDAY MORNING
NOVEMBER 8, 1959

8:00 a.m. Registration

Aaron Kellner, Presiding

9:00

1. Influence of Dietary Carbohydrate and Protein on Serum and Liver Cholesterol in Germ-Free Chickens

David Kritchevsky, Ruth R. Kolman, R. M. Guttmacher and Martin Forbes. From the Wistar Institute of Anatomy and Biology, Philadelphia, Pa., and the Department of Microbiology, Temple University School of Medicine, Philadelphia, Pa.

It has been shown that specific dietary carbohydrates have a distinct effect on the serum cholesterol levels of rats, rabbits or chickens. Thus, animals on a sucrose-cholesterol diet exhibit higher serum cholesterol levels than do those ingesting glucose plus cholesterol. Addition of a sulfa drug or antibiotic to the diet does not affect the serum cholesterol level of the sucrose-fed animals, but causes a marked rise (30-40 per cent) in the glucose-fed groups. To further test this effect, conventionally reared and germ-free chickens were given diets containing 3 per cent cholesterol and differences in dietary carbohydrate (glucose and sucrose) and dietary protein (casein or soybean protein) were compared.

The germ-free state enhanced the growth of the glucose fed birds (215 vs. 195 Gm.) but not of the sucrose group (177 vs. 180 Gm.). The chickens fed casein grew better than did those fed the soybean, and the germ-free state resulted in better growth in both groups. Average weights in the casein group (348 vs. 305 Gm.) and in the soy protein group (233 vs. 218 Gm.). In general, liver lipid levels paralleled the serum cholesterol levels in all groups.

9:15

2. Effects of Carbohydrates on Fat Absorption

Alexander Michajlik and J. H. Bragdon. From the Section on Metabolism, National Heart Institute, Bethesda, Md.

It has been reported that the alimentary lipemia which follows a fat meal in man can be abolished by the concomitant feeding of glucose. It was suggested that the most likely explanation of this phenomenon was a more rapid removal of chylomicrons from the blood stream, but it had been previously reported from this laboratory that the rate of removal of injected chylomicrons was not significantly different in carbohydrate-fed rats compared with fasting controls. The effects of carbohydrate on fat absorption were therefore investigated in the rat.

Animals have been fed olive oil with and without starch, sucrose, and glucose. Five hours later the

amount of oil remaining in the stomach was significantly greater in the carbohydrate-fed animals. The same delay in emptying time occurs during the intravenous administration of glucose.

Rats with cannulas in the thoracic ducts have been fed oil with and without carbohydrate, both orally and intravenously. Carbohydrate greatly reduced the fat content of hourly chyle collections. By injecting fat emulsions directly into the duodenum of such rats, and thereby avoiding the factor of delayed gastric emptying, it has also been demonstrated that intravenous glucose inhibits the absorption of fat from the intestine.

9:30

3. Effects of MER-29 on Tissue and Plasma Cholesterol Concentrations and on Hepatic Cholesterol Synthesis from Mevalonic Acid

R. Gordon Gould, E. H. Lilly, and V. E. Mitchell. From the Los Alamos Scientific Laboratory, University of California, Los Alamos, N. M.

Blohm et al. have recently reported that MER-29 (1-[p-(β-diethylaminoethoxy)-phenyl]-1-(p-tolyl)-2-(p-chlorophenyl)ethanol) decreases cholesterol concentrations in rat plasma and tissue to remarkably low values and inhibits cholesterol biosynthesis as measured by incorporation of acetate-C^{14} in vivo. We have found the synthesis of cholesterol from mevalonic acid-2-C^{14} in rat liver homogenates to be inhibited to about 15 per cent of the control value after feeding 2.5 mg. of MER-29 per 100 Gm. rat per day for 2 days. Addition of 1 mg. MER-29 to the homogenate from 5 Gm. of normal rat liver inhibited cholesterol biosynthesis from mevalonic acid by more than 90 per cent. These findings support the conclusion of MacKenzie and Blohm that the inhibitory effect occurs at a late stage, probably between some digitonin-precipitable sterol and cholesterol.

Male rats fed MER-29 at a level of 0.05 per cent of the diet for 42 days showed marked decreases (40-70 per cent), of cholesterol concentration in plasma, liver, adrenals, and intestine, and decreases of 20-30 per cent in the residual carcass values. Some slowing of weight gain was observed in younger rats but none in 300 Gm. rats. No other abnormalities or evidences of toxicity were observed.

Rats fed a diet containing 0.5 per cent cholesterol and 0.05 per cent MER-29 for 42 days gave cholesterol concentrations in plasma, liver, and other tissues almost as low as in rats fed MER-29 alone and far lower than would be expected in rats fed a 0.5 per cent cholesterol diet. These preliminary experiments suggest that MER-29 may be a powerful inhibitor of cholesterol absorption as well as an inhibitor of biosynthesis.

9:45

4. Observations Concerning the Site of Inhibition of Cholesterol Synthesis by MER-29

Mary L. Mobberley and Ivan D. Frantz, Jr. From the Cardiovascular Research Laboratory, Department of Medicine, Medical School, University of Minnesota, Minneapolis, Minn.

MacKenzie and Blohm have shown that when MER-29, 1-[(4-diethylaminoethoxy) phenyl]-1-(p-tolyl)-2-(p-chlorophenyl) ethanol, is given to rats, and the unsaponifiable lipids of the liver are labeled by administration of sodium acetate-1-C^{14}, most of the radioactivity of the unsaponifiable lipids is eliminated by purification via the dibromide. Experiments were undertaken to localize more accurately the site of this block in cholesterol synthesis.

Rats were maintained for 10 days on daily doses of 5 mg. of MER-29 given subcutaneously as a suspension in olive oil. Slices of the livers were incubated for 1 hour in sodium acetate-1-C^{14}, and the unsaponifiable lipids were chromatographed on silicic acid-Super-Cel. Radioactivity was associated with the various fractions from the column in the following precentages: squalene 12, lanosterol 15, 4-monomethylcholestenols 6, cholesterol 0, zymosterol-lathosterol 21, new higher counting companion, more polar than any of the above, 46. For an untreated control rat, the percentages were as follows: squalene 12, lanosterol 3, 4-monomethylcholestenols 2, cholesterol 58, zymosterol-lathosterol 25, new higher counting companion 0.

Liver homogenates from rats treated with MER-29 converted tritiated lathosterol to cholesterol in good yield, without the accumulation of tagged intermediates. The livers of treated rats accumulated large amounts of a sterol which behaved chromatographically and colorimetrically like zymosterol, as well as small but weighable amounts of the new companion. The block appears to involve the shift of the nuclear double bond from the 8 to the 7 position.

10:00

5. Comparison of a Direct Serum Procedure to Extraction Procedures for Measuring Serum Cholesterol

Robert V. Moore and Edwin Boyle, Jr. From the Lipid Metabolism Laboratory, Department of Medicine, Medical College of South Carolina, Charleston, S. C.

The many modifications of the classical Bloor method for determining cholesterol concentrations in serum with the consequential variance in "normal" results, plus the inherent errors of the many-step handling procedures for these extraction procedures led to a comparison of a direct procedure, with minimal handling procedures, to extraction procedures.

The direct serum cholesterol determination is a modification of the procedure of Zlatkis et al., with the color modification of Rosenthal et al., and will be presented briefly. The cholesterol values obtained will be compared to results obtained from extracted serum. The following facts have been established: 1. Cholesterol values obtained from extraction procedures tend to approach direct cholesterol values. 2. The difference in the values obtained by the various extraction procedures as done by the same personnel is small. 3. Multiple extraction procedures give higher values than single extraction procedures. 4. A high percentage of the cholesterol which is not extracted is usually found in the preparative ultracentrifuge fraction with a density $>$ 1.063 Gm. per ml., but proteins in other lipoprotein components may, and do at times, hold their lipid moieties so firmly as to prevent their complete extraction. 5. The unique character of the sera of individuals, as shown by a variability of extractability from 50-100 per cent, each individually reproducible, is clearly set forth. 6. The errors inherent to hemolysis and to physiologic concentrations of bilirubin, nicotinic acid, and the fat soluble vitamins A, D, E, and K have been studied and have been found negligible under normal conditions. These facts show that values obtained from direct serum determinations are more likely to represent the cholesterol moiety of serum. The direct serum determination method gives more consistent, reproducible, and reliable results. The direct test described is also much simpler, much more rapid, and less expensive to perform.

10:15

6. Comparative Quantitation of the Sources of Plasma Cholesterol in Dog and Man

Richard Abbuhl, C. Bruce Taylor, Dorothy Patton and George E. Cox. From the Department of Pathology, Presbyterian-St. Luke's Hospital, Chicago, Ill.

Suppression of hepatic, but not extrahepatic, cholesterol synthesis by dietary cholesterol, justifies considering these as separate sources of plasma cholesterol. Quantitation of their relative contributions is being attempted as follows: By continued administration of a diet containing large, known amounts of cholesterol, hepatic cholesterol synthesis is virtually eliminated in all species that have been adequately studied. Using labeled dietary cholesterol with known specific activity, the ratio of plasma cholesterol specific activity to dietary cholesterol specific activity will rise to a maximum which represents the fraction of plasma cholesterol derived from diet. This should equal the maximum hepatic contribution when no cholesterol is ingested. The remaining fraction of plasma cholesterol must derive from extrahepatic cholesterol synthesis. Morris et al. applied this principle to rats. We are applying it to man and other species. In dogs, the greatest contribution of dietary cholesterol to plasma cholesterol is obtained when egg yolk is used as a medium for administration; upon the continued administration of 3 Gm. cholesterol per day, about 90 per cent of plasma cholesterol comes from the diet. With human subjects, 5 Gm. cholesterol per day dissolved in margarine supplied 10 to 15 per cent of plasma cholesterol; higher percentages are expected from the study now in progress, where egg yolk is used instead of margarine.

10:30

7. On the Interpretation of Disappearance Curves of Radioactive Serum Cholesterol

Joel Avigan and Daniel Steinberg. From the Section on Metabolism, National Heart Institute, Institutes of Health, U.S. Public Health Service, Bethesda, Md.

A number of authors have measured the disappearance of fed or injected radioactive cholesterol from the serum compartment and have assigned a rate constant to this disappearance. More recently it has become clear that this disappearance is not a true first order process and therefore the "half life" of serum cholesterol is not a meaningful term. These studies in rats were undertaken to evaluate exchange processes between serum cholesterol and tissue cholesterol in various organs over extended time periods. Tracer doses of 4-C^{14}-cholesterol were fed to rats which were then sacrificed at intervals from 6 hours to 7 weeks. The specific radioactivity of cholesterol in the liver and small intestine paralleled that of the serum quite closely throughout the study. On the other hand, the specific radioactivity of cholesterol in the skeletal muscle, kidney and brain, while initially very low relative to that of the serum, was considerably higher at 7 weeks. By that time the ratios of specific activities of cholesterol in these tissues relative to that in serum were, respectively, 3.3, 5.9, and 1.8. The ratios

or lung and heart were 1.6 and 1.6. Studies in which rabbits were injected with biologically labeled lipoproteins gave similar results. Clinical studies were carried out in which both the serum disappearance curve of C^{14}-cholesterol and the net fecal excretion of cholesterol and bile acids were measured. The total excretion calculated from the apparent "half life" of serum cholesterol on the basis of the assumption that only the turnover of cholesterol in serum, red blood cells and liver is quantitatively significant was less than the excretion actually observed. Since the total amount of cholesterol in skeletal muscle, brain and some of the other tissues in which cholesterol turns over slowly is very large, it appears likely that the later phases of serum cholesterol disappearance curves in part reflect back exchange of radioactive cholesterol from these sources.

10:45

8. Lability of Cholesterol in Human Atherosclerotic Plaques

R. Gordon Gould, Richard J. Jones, and Robert W. Wissler. From the Los Alamos Scientific Laboratory, University of California, Los Alamos, N. M., and the Departments of Medicine and Pathology, University of Chicago, Chicago, Ill.

A previous report demonstrated that dietary cholesterol mixes with and becomes indistinguishable from the cholesterol of endogenous origin in the liver-blood pool. The cholesterol in this pool equilibrates with that in all tissues studied in experimental animals, except brain, but at widely varying rates. The question arises to what extent the cholesterol present in human atherosclerotic plaques is still capable of equilibration with blood cholesterol, since this will be an indication of the reversibility of the atherogenic process.

Tritium-labeled cholesterol was fed to a group of patients with poor prognoses (including some with myocardial infarction) at a constant daily dosage after a priming dose 10 times as large. This regimen was found to give almost constant plasma cholesterol specific activity values. The cholesterol concentration and specific activity were determined in samples of plasma, liver, the coronary, iliac and pulmonary arteries, samples of several parts of the aorta, and of various other tissues from all patients coming to autopsy. Results were generally in agreement with previous animal studies in showing most rapid equilibration of liver-blood cholesterol with spleen, intestine, lung, heart, adrenal, and kidney; less rapid with skeletal muscle and fat; and slowest with arteries. The more severely atherosclerotic samples of arterial tissue showed, in general, slower rates of equilibration but even those with cholesterol concentrations over ten times the normal values gave, in 1 case, 8 per cent equilibration in 4 days (mean of 3 samples) and, in a second case, 11 per cent in 14 days (mean of 3 samples).

One patient who took cholesterol-H^3 daily for 2 months and who died 5 months after the last dose showed essentially equal specific activity values in serum, liver, spleen, and thoracic aorta and 75 per cent of this value in abdominal aorta. Atherosclerosis score was 2+ in thoracic and 3+ in abdominal aorta. These results suggest that the cholesterol in human atherosclerotic lesions is interchangeable with blood cholesterol but at a very slow rate.

11:00

9. Origin of Various Lipids in Atheromatous Lesions of Rabbits

H. A. Newman and D. B. Zilversmit. From the Department of Physiology, University of Tennessee, Memphis, Tenn.

The finding that plaque phospholipid was synthesized by the arterial wall is based on studies with P^{32}. Since incorporation of P^{32} does not necessarily provide a valid index of synthesis of the fatty acid portion of the phospholipid molecule nor give any information on the synthesis of other lipids, C^{14}-acetate was employed in the present study. Albino rabbits on 1 per cent cholesterol intake for 3-4 months were either eviscerated (to suppress plasma-lipid synthesis) or sham operated. Thirty minutes to 5 hours after injection of C^{14}-acetate tissues were sampled for lipid analysis. All animals exhibited gross atheromatous lesions. The specific activity of atheromatous phospholipids in the eviscerates exceeded that in plasma in all animals by factors ranging from 10 to 74. Thus the C^{14} studies confirm earlier findings with P^{32} that a major portion of the labeled arterial phospholipid derives from synthesis in situ. Triglyceride specific activities in aorta also exceeded those in plasma, but cholesterol specific activities were too low to give reliable information. To trace the origin of aortic cholesterol several normal rabbits were placed on a constant intake of 1 per cent C^{14}-cholesterol in their diet until different degrees of atheromatosis were established. Multiple determinations of the specific activity of serum cholesterol and a final determination of aortic cholesterol specific activity were performed. Preliminary results indicate considerable deposition of plasma cholesterol or exchange between plasma and aortic cholesterol takes place.

11:15

10. Influence of Cholesterol Concentrations on Biosynthesis of Proteins in the Isolated Perfused Rat Liver

Paul S. Roheim, David E. Haft, Abraham White, and Howard A. Eder. From the Departments of Medicine, Biochemistry, and Radiology, the Albert Einstein College of Medicine, New York, N. Y.

It has been shown that the plasma lipoproteins can be synthesized both by rat liver slices and by the isolated perfused rat liver. Previous studies using the perfused rat liver have shown that prefeeding the liver donor rat with cholesterol results in marked inhibition of cholesterol biosynthesis but no inhibition of protein synthesis as measured by incorporation of uniformly labeled lysine C^{14}. X-radiation, 2400 r., to the liver donor rat resulted in an appreciable increase in cholesterol synthesis, but its effects on the synthesis of proteins in the lipoprotein fractions were less marked.

Measurements of lysine incorporation into the proteins of the high ($D > 1.063$) and low density ($D < 1.063$) lipoprotein fractions by rat livers perfused with plasma obtained from rats fed a high cholesterol diet for 13 days have been made. The cholesterol content of the perfusate was twice that in the control perfusions, and this was associated with an increase in the concentration of low density lipoproteins in the perfusate. In the three experiments completed, the specific activities of the high and low density lipoproteins were within the normal range, but the total incorporation of C^{14} was increased in the low density fraction but not in the high density fraction. Further investigation of the effects of altering the lipid content of the perfusion fluid are in progress.

11:30

11. Identification of Substances Responsible for Lipemia-Producing Activity of Pituitary Gland

Daniel Rudman, Floyd Seidman, and Maria B. Reid. From the Columbia Division, Goldwater Memorial Hospital, and Department of Medicine, Columbia University, New York, N. Y.

Previous reports from this laboratory have shown that a single injection into rabbits of unfractionated alkaline extract of 30-90 mg. of desiccated hog anterior pituitary lobes consistently produces a two to fivefold increase in serum lipids. No effect upon serum lipids is produced by the 6 recognized anterior lobe hormones when tested separately at doses equivalent to 500 mg. of the gland. However, a combination of ACTH with any of the other 5 hormones cause lipemia in about 50 per cent of rabbits when tested at doses equivalent to 200 mg. of gland. Combinations of hormones not including ACTH have no effect upon the rabbit's serum lipids.

Fractionation of crude pituitary extract by the method of Bonsnes shows that the major portion of the lipemia-producing activity can be separated from ACTH, growth hormone, and lactogenic hormone. Hog pituitary glands are extracted with 2 per cent NaCl solution at pH 7.6. The extract is adjusted to pH 4.5 and the precipitate removed. Fractional precipitation with acetone is then carried out. The major portion of the lipemia-producing activity is concentrated in the fraction precipitated between 75 per cent and 90 per cent acetone concentration. This material is further purified on an ion-exchange column. The final fraction has a lipemia-producing potency about 10 times greater than that of desiccated hog anterior pituitary lobes, and 7 times greater than that of the unfractionated anterior lobe extract.

ACTH has been shown to have a potentiating effect upon the production of lipemia. In addition, these observations suggest the existence of a separate lipemia-producing pituitary hormone.

11:45

12. Fecal Steroid Analyses in Man

R. S. Rosenfeld and Leon Hellman. From the Sloan-Kettering Institute for Cancer Research, New York, N. Y.

The major route for the elimination of cholesterol from the body is fecal excretion in the form of C-27 steroids and bile acids. The relative quantities of neutral steroids as compared to bile acids and the composition of the neutral steroids are of importance in investigation of mechanisms by which hypocholesteremic agents achieve their effects. Coprostanol, the principle fecal sterol, was presumed to be formed by the reaction pathway (1) cholesterol → cholestenone → coprostanone → coprostanol, but more recently we have shown by double-labeling techincs that the direct reaction (2) cholesterol → coprostanol is more likely. The analytic data to be presented, representing 55 determinations in 14 subjects on modern U.S. diets, provide further information concerning these two pathways.

The dry weight of feces was 9-56 Gm. (average 25) per day. The steroids were in the unconjugated form and constituted 4-10 per cent of the dry weight. The steroids were composed of 43-85 (average 66) per cent neutral steroids and 15-57 (average 34) per cent of bile acids. Chromato-

raphic separation of the neutral steroid fraction gave the following results: coprostanone, 4-11 per cent (average 6 per cent); coprostanol, 5-82 per cent (average 64 per cent); and cholesterol, 5-25 per cent (average 11 per cent). The cholesterol fraction contained 5-30 per cent (average 20 per cent) cholestanol. Separation of both the coprostanol and the cholesterol fractions into α and β sterols showed that over 90 per cent was contained in the β fraction. Cholestenone could not be detected. During the hypocholesteremic effect of corn oil, there was no increase in the excretion of either α sterols or bile acids, but a significant increase in the β sterol fraction. The absence of cholestenone may be taken as further evidence for pathway (2) or suggests that it may be in a very rapidly turning-over pool of minute size in pathway (1).

SUNDAY AFTERNOON

12:00 Luncheon
G. Lyman Duff Memorial Lecture: Dr. Paul Dudley White, "Atheroma and Thrombosis—Major Threats to Our Health Today."
2:00 Business Session
3:00 Presidential Address: James C. Patterson

Forrest E. Kendall, Presiding

3:30

13. Effect of Rate of Ingestion of the Diet ("Meal Eating" vs. "Nibbling") on Atherogenesis in Chickens

Clarence Cohn, Ruth Pick, and Louis N. Katz, with the assistance of Louisea Bell, Phillip Johnson and Dolores Century. From the Departments of Biochemistry and Cardiovascular Research, Michael Reese Hospital, Chicago, Ill.

Evidence suggesting that the rate of ingestion of the diet plays a significant role in the regulation of intermediary metabolism, and as a result, in over all body metabolism, has been summarized recently. As part of a long-term study of the metabolic alterations produced by changing nibbling animals to meal eating ones, the effect of these feeding habits on atherogenesis was evaluated in chickens. One group of birds was allowed to eat ad libitum ("nibbling") a diet containing 0.5 per cent cholesterol, 5 per cent cottonseed oil and 20 per cent protein and another group was presented with this diet for an hour in the morning and an hour in the afternoon ("meal eating"). After 5 experimental weeks, the animals were bled for serum lipid analyses and sacrificed for evaluation of gross aortic and microscopic coronary atherosclerosis. The "meal eating" chickens ate about one third less diet and gained about one third less body weight than the "nibblers." Mean serum cholesterol levels of the nibbling birds, which had eaten all night prior to sacrifice, was 294 mg. per cent; by contrast, the serum cholesterol of the "meal eaters," bled 18 hours after their last meal, was 584 mg. per cent. Grossly, the thoracic aortas of the "meal eaters" exhibited both an increased incidence (100 vs. 44 per cent) and severity (1.80 vs. 0.42) of atherosclerotic lesions. Microscopically, coronary atherosclerosis was present in 2.2 per cent of the vessels of the "nibblers" and in 14.6 per cent of the vessels of the "meal eaters." The results are interpreted to indicate that the rate of ingestion of the diet plays a role in atherogenesis.

3:45

14. Reduction of Plasma Cholesterol in Animals with Bile Acid Sequestrants

David M. Tennent, Henry Siegel, Mary E. Zanetti, Gunther W. Kuron, Walther H. Ott, and Frank J. Wolf. From the Merck Institute for Therapeutic Research, Rahway, N. J.

Present evidence indicates that the rate of oxidation of cholesterol is regulated by the need for bile acid in the enterohepatic cycle. Removal of bile acid from the enterohepatic cycle by introduction of a bile acid sequestrant into the intestine should increase the oxidative destruction of cholesterol.

We have studied the effect of feeding 2 high molecular weight polymeric quaternary ammonium salts on blood cholesterol in experimental animals. These compounds form insoluble or undissociated complexes with bile acids, but are not themselves digested or absorbed from the gut.

In short-term experiments plasma cholesterol rise in cholesterol-fed cockerels was inhibited 50 per cent by feeding these compounds as 1 per cent of the diet. In longer experiments cholesterol levels and plaque formation also were similarly reduced. In normocholesterolemic cockerels, fed basal diet, cholesterol concentrations were reduced from an average of 73 mg. per cent to 51 mg. per cent in 4 days.

In normal dogs cholesterol concentrations were reduced 25 per cent by sequestrant feeding from control levels near 100 mg. per cent. In experiments lasting as long as 1 year dogs fed sequestrants daily appeared to be alert and free from toxic effects. Hematological and biochemical tests made at intervals yielded normal results, except

for lowered plasma cholesterol levels. There were no signs during life or at autopsy of impaired fat absorption. At autopsy no pathologic changes attributable to sequestrant feeding were observed either grossly or on microscopic examination of the tissues.

4:00

15. Response of Man to Dietary Cholesterol

J. M. R. Beveridge, W. F. Connell, G. A. Mayer and H. L. Haust. From the Departments of Biochemistry and Medicine, Queen's University, Kingston, Ontario, Canada.

In 1958 we reported at the IVth International Congress of Biochemistry that one of the factors responsible for the hypercholesterolemic activity of butter fat was its cholesterol content. Further work utilizing homogeneous formula diets has demonstrated that the serum cholesterol level in man is in fact highly responsive to the concentration of dietary cholesterol. Ninety-three subjects (university students) were placed upon a homogenized fat-free diet for a period of 8 days at which time they were divided in 8 groups and given a diet modified by the substitution of a butter oil fraction for 30 per cent of calories at the expense of carbohydrate. The butter oil fraction represented approximately 60 per cent of the original butter, the more volatile triglycerides and essentially all of the cholesterol having been removed by distillation in high vacuum, a process very kindly carried out for us by the Distillation Products Industries. The amounts of added purified cholesterol in milligrams per 950 calories were as follows: Group 1, nil; 2, 25 mg.; 3, 50 mg.; 4, 100 mg.; 5, 200 mg.; 6, 400 mg.; 7, 800 mg.; and 8, 1,600 mg. Sixty-seven subjects successfully completed the experiment. The serum cholesterol values were found to increase with increasing dietary cholesterol up to between 200 and 400 mg. per 950 calories which corresponded to about 600-1,200 mg. per day. At dietary cholesterol levels of above 400 mg. per 950 calories the serum concentrations of the sterol plateaued. On the basis of these experiments there can no longer be any doubt of the responsiveness of man to dietary cholesterol although the nature of the accompanying fat or oil affects to a large extent the response obtained.

4:15

16. Cholesterol Metabolism in Methyl Testosterone-Treated Dogs

Liese L. Abell, E. H. Mosbach, and F. E. Kendall. From the Columbia University Research Service, Goldwater Memorial Hospital and the Departments of Biochemistry and Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y.

In 1957 Furman reported that oral administration of methyl testosterone (50 to 600 mg. per day) to dogs consistently lowered their serum cholesterol levels. We have studied the effect of methyl testosterone in dogs maintained on diets containing added fat and/or added cholesterol. When 200 mg. per day of methyl testosterone was given to dogs on low cholesterol diets providing 40 per cent of the calories as fat, the serum cholesterol levels dropped 51 per cent. In contrast, on high fat diets containing 2.5 per cent cholesterol, this dose of methyl testosterone increased serum cholesterol levels 39 per cent. Balance experiments were carried out in 2 dogs maintained on a stock diet. After a suitable control period the animals received 50 mg. per Kg. per day of methyl testosterone orally for 3 weeks and then were taken off the drug for another control period. Feces were collected daily throughout the experimental periods and analyzed for sterols and bile acids.

It was found that on the low fat, low cholesterol diet, the cholesterol excretion did not change in response to methyl testosterone administration. The bile acid excretion tended to rise during the period of drug administration, but did not return to control levels after the drug was withdrawn. Additional studies with dogs receiving diets high in fat and/or cholesterol are in progress and will be discussed.

4:30

17. Comparison of Effects of Butter and Egg Yolk on Development of Atherosclerosis in Swine

H. C. Rowsell, H. G. Downie, and J. F. Mustard. From the Ontario Veterinary College, Guelph, and Department of Medicine, Sunnybrook Hospital, University of Toronto.

An earlier study showed that swine develop some atherosclerosis on low fat diets. A diet containing 40 per cent of the calories as margarine does not accelerate the development of atherosclerosis while a diet containing 40 per cent of the calories as butter does. A further study has been done comparing the effects of egg yolk and butter on the development of atherosclerosis.

Thirty-three swine were divided into 3 matched groups of eleven. One group was maintained on the basic diet, a second group on the basic diet plus 33 per cent of calories as butterfat, a third group on the basic diet plus 33 per cent of calories as egg yolk. All diets were isocaloric. The animals were studied at intervals during the experiment. The indicies followed were: Clearing factor activ-

ty, cholesterol and phospholipid levels, lipoprotein, and coagulation indicies. Swine were sacrificed at intervals and the amount of atherosclerosis graded with respect to gross and microscopic appearances.

The butter diet accelerated the rate of development of atherosclerosis but was not associated with much change in the indicies followed except for some clotting tests. The feeding of egg yolk caused elevation of blood lipids in all animals, a variable change in clearing factor activity, a shift in the lipoproteins and an increase in the activity of some clotting indicies. The butter fed swine showed moderate acceleration of the rate of development of atherosclerosis, while the animals on egg yolk showed marked acceleration of the rate of development of atherosclerosis. These observations indicate that egg yolk is considerably more important than margarine or butter in accelerating the rate of development of experimental atherosclerosis and causing changes in various biochemical indicies.

4:45

18. Effects of Material Rich in Phosphatidyl Ethanolamine or Phosphatidyl Serine on Clotting and Cholesterol Levels

J. F. Mustard, H. G. Downie, H. C. Rowsell, and A. Bier. From the D.V.A. Sunnybrook Hospital, Toronto, Department of Medicine, University of Toronto, and Ontario Veterinary College, Guelph.

Fractions rich in phosphatidyl ethanolamine (PE) and rich in phosphatidyl serine (PS) were prepared from beef, swine and human brain and liver by modifications of Folch's technics. Using the thromboplastin generation test, PE was active in thromboplastin formation, while PS over the same range of dilution was inactive. PS in concentrations 0.1 that of PE inhibits the activity of the latter phospholipid in this test. Addition of PE to blood as it clots accelerates the rate of loss of AHG activity, and thrombin formation while addition of PS slows the rate of fall in AHG activity, and thrombin formation. These in vitro studies indicate that PE rich material accelerates clotting and PS rich material inhibits clotting.

The in vivo clotting effects were studied using swine. Intravenous PE increased Christmas factor (PTC) activity, decreased AHG activity and the circulating platelet count, accelerated the Russell viper venom time (RVVT) and clotting time. Intravenous PS decreased Christmas factor activity, prolonged the clotting time and prothrombin time, but accelerated the RVVT. There was little change in the platelet count and AHG activity. Therefore, intravenous PE accelerates the thromboplastin mechanism, whereas PS inhibits this mechanism. PS appears to inhibit Christmas factor and factor VII activity. Since the RVVT is accelerated in vivo under the conditions where there is an anticoagulant effect, some doubt is cast on the validity of this test as an index of accelerated clotting.

Administration of 5 to 15 Gm. per day of PS rich material to 5 subjects receiving 35 per cent of their calories as animal and vegetable fat lowered the cholesterol level by 10 to 20 per cent. PE had no effect. Therefore, PS rich material can have as well as an anticoagulant effect a hypocholesterolemic effect.

MONDAY MORNING
NOVEMBER 9, 1959

Robert H. Furman, Presiding

9:00

19. Histochemical Studies of Cerebral Arteries

Frederick T. Zugibe and Kenneth D. Brown. From the Geriatrics Research Project, Veterans Administration Hospital, Downey, Ill.

Histochemical studies of the cerebral arteries have been grossly neglected. The following is a preliminary report of our observations on grossly normal and early lesions of cerebral arteries of individuals ranging from fetuses to 65 years of age. Newer embedding technics utilizing carbowax which have been recently developed in our laboratory produce sections with minimal lipid loss, allow routine stains to be applied to adjacent sections, and further permit the observations of both lipid and acid polysaccharide on the same tissue section.

There is no relationship between acid mucopolysaccharides (AMP) and lipids in respect to staining intensity and/or distribution in any of the age groups studied.

Lipid was essentially absent in the fetuses. Occasionally slight lipid tinting was observed in the internal elastic membrane of juveniles. The most striking observation in the adults was the presence of lipid in the internal elastic membrane and reduplication of elastic elements in the intima.

Data from adjacent sections cut at 1 μ and stained for lipid supported our previously reported observation on aortas that the lipid was within the fiber and not physiologically oriented on the outside surface. In fetuses and infants there was an increase in testicular hyaluronidase hydrolyzable AMP principally in the proximal medial surface. In the adults there was an increase in testicular

hyaluronidase resistant AMP in the proximal media and in the intima. This increase in AMP corresponded to the areas of collagen increase. Fragmentation, fraying, and reduplication of the internal elastic membrane was rarely present in the fetuses and infants. This would suggest that there is no relationship between the presence of AMP and these elastic changes.

In adults, reduplication of the internal elastic membrane was frequently observed principally in the region where the intima was thickest. The significance of these observations will be discussed.

9:15

20. Vascular Lesions Induced by Serotonin and Adrenalin

Takio Shimamoto. From the Department of Clinical Physiology, Tokyo Medical and Dental University, Yushima, Bunkyo-ku, Tokyo, Japan.

Recently, we succeeded in producing a fibrinous type of atheroma with regular complications of myocardial infarct-like lesions, and encephalomalacia in rabbits. Cerebral hemorrhage occurred from venules located specifically in the thalamostriatal region. These hemorrhages closely resemble cerebral hemorrhage seen in hypertensive patients. These lesions are being produced by combinations and interaction of serotonin and adrenaline. These lesions are produced with great regularity.

9:30

21. Nature of Lipid Material in Involved Areas of Human Aortas

M. Sugai, T. Nishida and F. A. Kummerow. From the Department of Food Technology, University of Illinois, Urbana, Ill.

Lipid material which could not be extracted with fat solvents was found in the involved, but not in the uninvolved portions of the intima stripped from human aortas. This lipid material could only be freed by mild saponification with alkali.

The lipid material in symplexes, which are formed in vitro by the interaction of various proteins such as blood serum or a solution of egg albumin and oxidized oil, could also not be removed by solvent extraction but could be freed by saponification with alkali, thus showing a similarity in properties between the lipids extracted from involved areas of the intima and the lipids in symplexes.

We, therefore, studied the interaction between fatty peroxides and the β-lipoproteins in human blood. The results indicated that the analytical centrifugal pattern of the β-lipoproteins in human blood became more heterogeneous after contact with fatty peroxides. A gradual increase in the S_f value was noted and the area under the lipoprotein peak gradually decreased. The chemical nature of this interaction and symplex formation will be discussed.

9:45

22. Composition of Fatty Acids in Cholesterol Esters Derived from Normal and Abnormal Intima

N. T. Werthessen, W. R. Nelson, A. T. James and R. L. Holman. From the Southwest Foundation for Research and Education, San Antonio, Tex., Medical Research Council, National Institute for Medical Research, London, England, and the L. S. U. School of Medicine, New Orleans, La.

Areas of normal and abnormal tissue were first delineated then cut from human aortas. The intima was stripped from the media. The pools of medial and intimal tissue were extracted separately. The cholesterol esters were isolated, purified, and then hydrolysed. The fatty acids were analyzed by gas liquid chromatography.

Material from 1 young woman and an older man has been analyzed at the time of submission of this abstract. There is no significant difference in the fatty acids of the cholesterol esters of the media; whereas significant differences are seen in the intima.

These can be grossly described as: 1. A higher proportion of the longer chained fatty acids are found in esters from abnormal tissue than in those from normal tissue. 2. Although they are minor components; an absence of acids shorter than C^{11} in cholesterol esters from abnormal tissue is seen as compared with the presence of such acids in normal intima. 3. A marked drop (from 18 per cent in normal tissue, to 3 per cent in abnormal) in the linoleic acid percentage composition was seen in the older patient whereas there was no difference seen in the younger patient between abnormal and normal intima. 4. The presence in 1 patient of a significant percentage (17 per cent of a presently unidentified long-chained (C^{20} or more) multisaturated fatty acid in the esters derived from the abnormal tissue. This acid if present in normal tissue could only have been present in very minute quantities.

These data are sufficient to show that the cholesterol esters derived from abnormal intima are chemically different from those derived from the normal intima of the same individual. It is expected that further analyses, perhaps sufficient to show an age trend will be available for presentation at the meeting.

10:00

23. Further Studies on Spontaneous Atherosclerosis in Pigeons

H. B. Lofland, T. B. Clarkson, R. W. Prichard and M. G. Netsky. Winston-Salem, N. C.

The White Carneau, Silver King, and Autosexing King pigeons develop spontaneous atherosclerosis on grain diets, unsupplemented with fat or cholesterol. Grossly and microscopically, the lesions resemble those of human beings. Show Racer pigeons, maintained under identical conditions, were practically free of atherosclerosis.

Six to 9-months-old White Carneaux were free of atherosclerosis, whereas 60 per cent of 12-month-old birds had lesions. Aortic plaques were observed in 89 per cent of the 18-24-month-old birds. All birds over 36 months of age were atherosclerotic. No differences in levels of serum cholesterol, phospholipid or total lipid were observed in the various age groups. The levels of aorta cholesterol rose strikingly at 24 months.

When young pigeons of resistant and susceptible breeds were fed fat and cholesterol, onset of the disease was accelerated in susceptible breeds; nonsusceptible breeds appeared more resistant to cholesterol feeding.

The extent of coronary atherosclerosis was determined by examining sections at intervals of 200 μ from the apex to the base of the heart of 20 7-year-old White Carneaux; 70 per cent had coronary artery lesions, with the same morphologic components as aortic lesions.

When isolated aortas from resistant and susceptible breeds were incubated in vitro with acetate 1-C^{14}, radioactivity was recovered in the total lipid extract, and in a digitonin-precipitable material. The two breeds were similar in amounts of acetate incorporated. In most cases the distal end of the aorta showed a higher rate of acetate incorporation than the proximal end.

10:15

24. Breed Susceptibility in Rabbits to Hypercholesterolemia and Atherosclerosis

DeWitt Hendee Smith and Elizabeth Gaman. From the New Jersey Neuro-Psychiatric Institute, Princeton, N. J.

Investigators using rabbits in atherosclerosis research often are annoyed at the variation of response encountered. Reports seldom state the breed of rabbit used. To assess this factor we fed 1 per cent cholesterol for 4 weeks to litters of different rabbit breeds and hybrids. Results have been so unexpected and striking that we are making this preliminary report.

Within litters cholesterol variation was itself variable, so that in Flemish Giant and New Zealands cholesterols were highly scattered. In the other litters cholesterols were more closely grouped. The mean cholesterols, distributed more normally, ranged from 749 ± 293 for the Flemish to 1636 ± 182 for the New Zealand-Californian cross.

The kind and extent of atherosclerosis gave some surprises. All but 2 of the litters showed typical atheromatous plaque deposits in the aorta varying somewhat within and between litters. Among these the New Zealands showed more and the Californian and New Zealand-Californian hybrids and intermediate atheroma, the chinchillas somewhat less. On the basis of amount or uniformity, there was no great preference. However the Flemish with low and highly variable cholesterol levels, showed a uniform wrinkling of the aortic intima, seemingly unique to this breed, which was confirmed microscopically as thin lipid deposit, but no plaques were present. The Dutch, with the least variation in cholesterol level, showed no aortic change whatever. The New Zealand-Californian hybrid had the highest cholesterol, low variability, good plaque formation and many other laboratory advantages.

Hybridization with selected parents may prove a useful way in which to cut down rabbit variability.

10:30

25. Cholesterolemia, Occupation, Physical Activity and Diet in the Middle-Aged Employees of a Chicago Utility Company

Jeremiah Stamler, Howard A. Lindberg, David M. Berkson, Wilda A. Miller and Marilyn Paganin. From the Heart Disease Control Program, Chicago Board of Health and the Department of Medicine, Northwestern University Medical School, Chicago, Ill.

During 1958, analyses of serum cholesterol were accomplished on over 90 per cent of the labor force aged 40-59 of a Chicago utility company. The mean values for 1,859 men and 170 women were 237 and 241 mg. per cent respectively. A minority of both sexes had values below 225 mg. per cent. Twenty and 25 per cent of the men and women respectively had values of 275 mg. per cent or greater; 9 per cent and 14 per cent, of 300 mg. per cent or greater. Little or no correlation was observed between cholesterol and weight-blood pressure levels. When the male population was stratified based on occupational and other sociological criteria—e.g., professional-executive-managerial-supervisory-technical personnel; clerical-sales; foremen; skilled-semiskilled and unskilled laborers; sedentary and nonsedentary employees;

salary and wage; indoor and outdoor; white- and blue collar; more and less educated; veteran and nonveteran—differences in cholesterol levels for the subgroups were generally insignificant. Prevalence rates for obesity and hypertension were also similar in the subgroups, as were patterns of diet and physical activity off the job. These data are consistent with the findings on occurrence rates of coronary heart disease in these subgroups of middle-aged working men.

10:45

26. Epidemiology of Atherosclerotic Lesions

Henry C. McGill, Jr., Jack P. Strong, Russell L. Holman, and C. A. McMahan, Louisiana State University, New Orleans; Carlos Tejada, Instituto de Nutricion de Centro America y Panama, Guatemala; Carlos Restrepo, Universidad del Valle, Cali, Colombia; Egon Lichtenberger, Hospital San Juan de Dios, Bogota, Colombia; and Lorenzo Galindo, University of Puerto Rico, San Juan, Puerto Rico.

Quantitative evaluations of coronary and aortic atherosclerotic lesions were compared in males 20-59 years necropsied in 4 geographic areas and representing 5 different population groups. Differences in fatty streaks from 1 group to another (maximum variation, twofold) were much less than variations in fibrous plaques (variation up to fivefold). For example, in coronary arteries 40-59 years of age, the average percentages of intimal surface covered by fibrous plaques were as follows: New Orleans white, 16; New Orleans Negro, 13; Puerto Rican, 10; Colombian, 4; and Guatemalan, 4. These values for coronary fibrous plaques are strongly correlated with percentages of natural deaths due to ischemic heart disease in the various necropsy groups, while values for fatty streaks are not. Thus the earliest stage of atherosclerotic lesions that can be statistically associated with ischemic heart disease on a group basis is the fibrous plaque. These and previous studies lend support to the idea that fatty streaks (as measured in this manner) are only slightly influenced by environment, while fibrous plaques may be predominantly determined by environment. The possibility remains that the qualitative lipid composition of fatty streaks, which may be environmentally determined, could account for the differences in fibrous plaques.

11:00

27. Vascular Lumen and Blood Flow

Simon Rodbard. From the University of Buffalo Chronic Disease Research Institute, Buffalo, N. Y.

These studies were undertaken to examine mechanisms involved in the regulation of the cross-section area of vessels. A single carotid artery was completely ligated in dogs and rats. Findings in the untouched contralateral artery were of special interest: Within 3 days an arc of the internal elastic membrane became fragmented, and macrophages containing elastica-staining material became evident at this site; collagen fibrils filled the arc, and an endothelial "plaque" appeared at the site. The ligated arteries showed progressive reduction of the lumen as a result of subendothelial proliferation and endothelial infolding. These findings may be interpreted as follows: Blood flowing through a vessel produces a mechanical drag on the endothelium, in accord with the velocity of the stream. Ligation of one carotid artery tends to increase the volume and velocity of blood flow in the contralateral carotid. The increased drag on the endothelium leads to lysis of an arc of the internal elastic membrane, followed by reconstruction of the vessel around a larger lumen in which the flow velocity and drag are returned to normal levels. Diminution in flow reduces velocity and drag; this is followed by subendothelial proliferation, infolding of the lining, and ultimate reorganization of the vessel around a reduced lumen. These findings suggest that the velocity of blood flow and the consequent drag on the boundary layer between blood and lining may play a role in the regulation of the cross-section area of blood vessels.

11:15

28. Thrombotic and Inflammatory Origin of Arteriosclerosis

Robert H. More and M. Daria Haust. From The Department of Pathology, Queen's University, Kingston, Ontario, Canada.

There is evidence in man and animals of a relation between serum lipids and the accumulation of lipid in the intima of the aorta and its immediate branches. It is however, not so apparent that there is such a relation between serum lipids and the pleomorphic intimal disease traditionally designated by the term arteriosclerosis. Some 1,300 sections of lesions from 150 aortas and the coronary arteries of 100 hearts, were examined in this study. A variety of stains and histochemical procedures were carried out on additional slides cut from these sections. In some instances it was apparent that the lesions did not start from a deposit of grossly or microscopically visible lipid. Many lesions were initiated and many progressed by means of inflammation of the intima and or thrombosis. Progression was characterized by fibrosis of these lesions and repeated episodes of inflammation and thrombosis. These studies were not designed to evaluate the role of serum lipids in the

initiation and progression of these lesions. However if serum lipids are important in the etiology and pathogenesis of any or all stages of the pleomorphic disease arteriosclerosis, then it would appear that one of the ways they act is by producing either inflammation, or thrombosis or both.

11:30

29. Papain Atherosclerosis

Fiorenzo Paronetto and David Adlersberg. From The Mount Sinai Hospital, New York, N. Y.

The well-established effects of papain on the ground substance suggested a study of prolonged papain administration upon the arterial tree in old and young rabbits. The old group consisted of 20 "old breeders," approximately 3 years old with a body weight of 4-5 Kg. The young group included 7 animals approximately 1-month-old with body weights ranging from 1.2 to 1.7 Kg. Each animal received 3 times weekly an intraperitoneal injection of papain in physiologic saline solution. The duration of the experiments varied from 15-60 days. All animals received Purina chow and water ad lib.

Fifty per cent of the "old breeders" presented unusual changes in the aorta consisting of slightly elevated white plaques varying from 0.2 to 0.3 cm. in diameter. Some of these plaques were isolated and discrete while others showed confluence which resulted in longitudinal streaks and larger areas of atheroma-like appearance. The plaques were seen in the ascending aorta, in the arch and, in the severe cases, in the distal aorta to the bifurcation of the iliac arteries. Although considerable variations were seen among the animals, the severity of the lesions seems to parallel the duration of papain administration. Two animals showed dissecting aneurysms of the aorta with hemorrhage into the wall. In contrast to the "old breeders," the "young" group showed no gross aortic lesions.

Histologically, the lesions presented severe changes in the media and intima with accumulation of metachromatic material and calcium but without any accumulation of lipid. Extensive fragmentation and coarsening of the elastic fibers were seen.

Thus, prolonged parenteral administration of papain produced striking gross and histological changes in the aorta in old rabbits.

11:45

30. Fatal Myocardial Infarction in Rhesus Monkeys with Diet-Induced Hypercholesterolemia

C. Bruce Taylor, George E. Cox, Marjorie Counts and Nelson Yogi. From the Department of Pathology, Presbyterian-St. Luke's Hospital, Chicago, Ill.

In earlier studies we reported the development of atheromas in the coronary arteries and the aorta and its major branches in Rhesus monkeys when mean cholesterol levels were maintained between 256 and 393 mg. per cent for 6 months or more. Hypercholesterolemia was induced by feeding an adequate diet containing 22 per cent butter fat and supplying 1.5 Gm. of cholesterol per day. Two female animals on this diet showed a marked propensity for hypercholesterolemia. They were maintained on this diet for 3 and 4 years and had mean serum cholesterol levels of 659 and 554 mg. per cent. Both animals developed cutaneous xanthomas on the hands and feet. One animal died from massive myocardial infarction. Five thrombotic occlusions showing various stages of organization were found in the coronary arteries. The coronary arteries also showed marked athero-arteriosclerotic narrowing, medial degeneration with fibrosis, calcification or foam cell infiltration, markedly increased medial vascularization and focal areas of secondary arteritis. The similarity to human coronary arteriosclerosis was striking. The other animal developed gangrene of her left lower extremity requiring a midthigh amputation. The arteries from the amputated extremity revealed atherosclerosis, medial degeneration and thrombosis. Arteriosclerotic lesions in the aorta and many other vessels also showed a striking similarity to human lesions.

MONDAY AFTERNOON

C. Bruce Taylor, Presiding

1:30

31. Anticoagulant Activity of Human Arterial Mucopolysaccharides

J. E. Kirk. From the Division of Gerontology, Washington University, St. Louis, Mo.

Extraction of acid mucopolysaccharide material was made from the intima-media layers of 27 samples of the descending thoracic aorta by the procedure of Dyrbye and Kirk. The age of the subjects from whom the samples were obtained ranged from 3 to 76 years. Analysis of the isolated material showed the following average percentage composition: SO_4, 12.5; hexosamine, 24.2; uronic acid, 33.5. Eighty per cent of the hexosamine was galactosamine and 20 per cent glucosamine. No significant change with age in

the sulfate content of the samples was found. Analysis of the electrophoretically separated fractions failed to reveal the presence of α-heparin in the material.

The anticoagulant activity of the mucopolysaccharide samples was determined by the procedure of Freeman, Engelberg, and Dudley. Each of the 27 samples was tested at 4 different levels by addition of 100, 200, 400, and 800 μg. of the material, dissolved in 0.9 per cent NaCl solution, to aliquots of the plasma. For comparative purposes a coagulation time test with heparin sodium, U.S.P., added in quantities of 0.4, 0.8, 1.2, 1.6, 2.0, and 2.4 μg. was run with each set of experiments.

The average coagulation times observed for 0, 100, 200, 400, and 800 μg. of mucopolysaccharide material were, respectively, 5 $\pm$ 0.1, 11.8 $\pm$ 0.2, 16.1 $\pm$ 0.3, 23.3 $\pm$ 0.4, and 34.2 $\pm$ 0.8 minutes. These observations show that the arterial mucopolysaccharide material possesses a definite, but low anticoagulant activity. When compared on a weight by weight basis, the anticoagulant activity of the material was less than 1 per cent of that exhibited by heparin sodium (α-heparin). The anticoagulant activity of the samples from children was moderately higher than the activity recorded for samples from adults.

The observed anticoagulant activity of human arterial mucopolysaccharides may constitute a factor of significance in connection with Duguid's theory concerning the etiology of atherosclerosis.

1:45

32. Functional Activity of Arterial Mucopolysaccharides

Ira Gore and Bernard J. Larkey. From the Veterans Administration Hospital, West Roxbury, Mass. and the Department of Nutrition, Harvard School of Public Health and the Department of Pathology, Harvard Medical School, Boston.

It has been suggested that altered distribution of intimal acid mucopolysaccharides with atherosclerosis depicts a parallel alteration in the anticoagulant property of the intima which may underlie the occurrence of thrombosis as a complication of atherosclerosis. In pursuit of this thesis, human aortas were extracted for acid mucopolysaccharides using a modification of the technics of Dyrbye and Kirk. Such extracts (MPS) proved to have anticoagulant properties similar to but less potent than those displayed by heparin. Neither substance displayed fibrinolytic activity when applied to clots of recalcified plasma. Since heparin also stimulates the formation of lipid clearing factor when given intravenously, aortic MPS preparation was tested for and shown to have similar activity in white rats.

Chemically, the acid mucopolysaccharides isolated from beef aorta have been identified as chondroitin sulfates A and B, hyaluronic acid and heparitin sulfate. Chondroitin sulfate B has previously been shown to be an anticoagulant and except for quantitative differences displayed the same reactions as the aortic MPS when tested for anticoagulant properties, for lipid clearing factor stimulation, and for fibrinolytic effect. Hyaluronic acid and chondroitin sulfate A proved to be completely inert when tested by the same procedures. Although heparitin sulfate was not available for similar evaluation, the identity of the reactions of CSA-B and aortic MPS seems to suggest that the demonstrable anticoagulant lipid clearing stimulatory properties of the latter (MPS) are due to its content of the former (CSA-B).

2:00

33. Effect of Heparin on Serum Cholesterol and Triglycerides, Fecal Bile Acids, and Digitonin-Precipitable Sterols

H. Engelberg. From the Division of Laboratories, Cedars of Lebanon Hospital, Los Angeles, Calif.

The main channels of cholesterol excretion are via the fecal bile acids and fecal cholesterol (or its bacterial degradation product, coprosterol). Accordingly, these analyses were done, together with determinations of serum cholesterol and triglycerides, in human volunteers upon their normal diets before and after the administration of heparin (300-400 mg. daily in divided doses). The control and experimental periods of observation were 4-6 days each. It seemed valuable to determine the effect upon cholesterol excretion of enhanced triglyceride clearance from the bloodstream.

Daily bile acid excretion was increased during the period of heparin administration in all 4 subjects, the increase varying from 21-112 per cent. At the same time a decrease in fasting serum triglycerides and cholesterol occurred. The results demonstrate that cholesterol excretion is increased and serum cholestrol decreased, when serum triglyceride removal is facilitated by injected heparin. This is further evidence that one of the functions of circulating cholesterol is to aid in the transport of alimentary neutral fat, and that one of the causes of an increased cholesterol level is a protracted elevation of serum triglyceride. The results also indicate that an increase in bile acid excretion, such as occurs after the substitution of unsaturated for saturated fats

n the diet, cannot necessarily be ascribed to an ffect upon cholesterol excretion, per se, since it ay also result from changes in a prior stage f fat metabolism.

:15

34. In Vitro Effects of Heparin on Human Blood Lipoproteins

Daniel A. Sherber and Martin Marcus. From he Metabolic Research Laboratory, Fordham Hospital, New York, N. Y.

In studying the ease of extraction of lipoprotein cholesterol(REC), the observation was made that in vitro heparinized human plasmas (50 mg. per 100 ml. whole blood) usually demonstrated much higher values than untreated serum. At refrigerator temperature, approximately 27 per cent of the cholesterol is extracted by the alcohol-ether system after 20 hours compared to 6 per cent with no heparin added. Serum and other plasmas obtained by using other anticoagulants (sodium citrate, potassium oxalate, and double oxalate containing potassium and ammonium oxalates) all have equal REC values (6 per cent). Electrophoresis of the hydro-alcoholic residue showed that the REC method removes all the lipid from protein although only a small fraction diffuses into ether. The effect of heparin is to increase the rate and amount of diffusing lipid. This effect seems to depend on the ability of heparin to alter the gel-forming tendency of serum. Previous reported studies indicated a possible adrenal factor affecting lipid and protein binding. The relationship between this and the findings with heparin will be discussed.

2:30

35. Lipoprotein Lipase and Serum Lipids in Experimental Biliary Obstruction

Saul P. Baker, Piero P. Foà, Paul B. Szanto, and Alvin Dubin. From the Departments of Medicine, Physiology and Pharmacology, The Chicago Medical School, and the Department of Pathology and Hekteon Institute for Medical Research of the Cook County Hospital, Chicago, Ill.

An increased heparin-activated lipoprotein lipase response in Laennec's cirrhosis has been reported. A markedly decreased lipoprotein lipase response in obstructive juandice was also reported. In order to more precisely evaluate lipoprotein lipase response in obstructive jaundice and correlate this response with serum lipids, the common bile duct was completely ligated in 7 normal dogs. Lipoprotein lipase response was determined and hepatic status and serum lipids were comprehensively evaluated on all dogs at weekly intervals after ligation. Control studies, including BSP excretion, were performed weekly on 6 of the dogs during a 3 week period prior to surgery.

A markedly decreased lipoprotein lipase response was observed in all 7 dogs after complete common bile duct ligation, thus confirming the decreased response in obstructive jaundice in man. Generally, lipoprotein lipase response was inversely proportional to total serum lipids, total serum cholesterol, esterified cholesterol, and lipid phosphorus levels. However, in 4 of the 7 dogs, sustained hyperlipemia (as high as 2,880 mg. per cent) and hypercholesterolemia (as high as 430 mg. per cent) were present for 2 to 5 weeks prior to the initial decrease in lipoprotein lipase. Hyperbilirubinemia, per se, did not appear to influence lipoprotein lipase response. In all 5 dogs that survived surgery by 4 weeks or more, a subsequent marked increase in lipoprotein lipase response was observed. This was generally, but not always, accompanied by a marked decrease in total lipids, total and esterified cholesterol, and lipid phosphorus. Postmortem microscopic examination of the livers of these animals revealed obstructive cholestasis and portal fibrosis.

It is suggested that the decreased lipoprotein lipase response in biliary obstruction is related to chronic cholestasis, and, indirectly, to serum lipid levels. The subsequent increase may be attributed to loss of hepatic parenchymal cells due to portal fibrosis.

2:45

36. Observations on Components of the Plasma Clearing System

J. L. Koppel, Lillian V. Novak, and John H. Olwin. From the Coagulation Laboratory, Department of Surgery, Presbyterian-St. Luke's Hospital, Chicago, Ill.

In vitro studies of human plasma clearing activity have been carried out in the presence and absence of purified human clearing factor preparations. The data obtained suggest that in only 25 per cent of all patients having little or no "inherent" plasma clearing activity is this deficiency due to a lack of the clearing enzyme proper. In the remaining 75 per cent it is caused by either the lack of a plasma cofactor or the presence of a clearing factor inhibitor or both. Although a distinct plasma cofactor appears essential for clearing as shown by the latter's disappearance as a result of ether treatment, no lack of this cofactor could be demonstrated in plas-

mas having deficient activity. However, these activities can be largely or completely restored by: (1) Adsorption of plasma with barium sulfate, (2) addition to plasma of citrate, oxalate, Na-versenate, or certain sulfhydryl inhibitors, and (4) heparin, polyethylene sulfonate or manuronate. The results suggest that, in these cases, the deficiency is due to excessive inhibitor levels and that the inhibitor may require free sulfhydryl groups. Data obtained with a variety of other metal versene salts indicate that calcium may also be essential for its action. It is of interest in this connection that of various purified coagulation factors studied only Ac-globulin (factor V) preparations strongly inhibit plasma clearing activity. Although some of the apparent characteristics of the clearing factor inhibitor are similar to those of Ac-globulin no evidence as to their possible identity has been obtained.

3:00

37. Quantitative Immunologic Differentiation of Human Serum β-Lipoprotein Fractions: Studies in Recent Myocardial Infarction

Saul P. Baker and A. S. Markowitz. From the Department of Medicine, The Chicago Medical School, and the Hektoen Institute for Medical Research of the Cook County Hospital, Chicago, Ill.

Production of antiserum to an ultracentrifugally-derived serum fraction from dogs on a thiouracil-cholesterol atherogenic dietary regimen has previously been reported. Subsequently, the serum fraction used as antigen was found to consist of a β-lipoprotein spectrum S_f 2-30 containing 3 peaks (S_f 3-7, S_f 8-11 and S_f 12-17) in dogs on atherogenic diets. In normal dogs, only one peak (S_f 3-7) was observed. Production of antiserum to this S_f 2-30 spectrum, and its use in precipitin tests was subsequently reported. However, quantitative immunologic differentiation of β-lipoprotein fractions has not been accomplished heretofore.

Using pooled sera freshly obtained from patients with recent myocardial infarction, it has been possible to quantitatively extract S_f 10-100 (fraction I), S_f 5-15 (fraction II), and S_f 3-9 (fraction III) lipoprotein fractions in bulk employing a dextran sulfate complex and the ultracentrifuge. These fractions were then used as antigens in rabbits to produce antisera. Specificity of each antiserum was established by differential absorption with the other 2 β-lipoprotein fractions. Quantitative determination of β-lipoprotein protein nitrogen for each fraction in whole sera tested was accomplished by micro-Kjeldahl analysis of precipitates.

Observations to date on a group of 44 patients with recent myocardial infarction yielded a mean of 1.44 mg. per cent protein nitrogen (range 0.9 to 1.70) for fraction I; a mean of 0.80 mg. per cent protein nitrogen (range 0.62 to 1.05) for fraction II; and a mean of 4.72 mg. per cent protein nitrogen (range 3.96 to 5.10) for fraction III. Six normal subjects yielded a mean of 0.62 mg. per cent protein nitrogen (range 0.4 to 0.72) for fraction I; a mean of 0.42 mg. per cent protein nitrogen (range 0.38 to 0.49) for fraction II; and a mean of 2.36 mg. per cent protein nitrogen (range 2.01 to 2.70) for fraction III.

It is suggested that quantitative immunologic studies of the protein moieties specific to fractions of ultracentrifugally-defined human serum β-lipoproteins may be useful in evaluating coronary atherosclerosis in man.

3:15

38. Immunochemical Reactions of Low Density Lipoproteins of Human Serum and Aortic Wall

Herbert J. Kayden, Beatrice C. Seegal, and Konrad C. Hsu. From the Department of Medicine, New York University College of Medicine, and the Department of Microbiology, Columbia University College of Physicians and Surgeons, New York, N. Y.

We have previously reported that saline extracts of homogenized portions of human aortic intima contain lipoproteins that can be fractionated by electrophoresis or ultracentrifugation. The phospholipid composition of β-lipoproteins (electrophoresis) and low-density lipoproteins (ultracentrifugation specific gravity < 1.063) of human sera have been compared with the phospholipid composition of comparable fractions isolated from aortic wall extracts. Although these lipoproteins are very similar in their physical properties, chemical analysis by silicic acid column chromatography and by differential alkaline hydrolysis, revealed striking differences in phospholipid composition.

Rabbits were immunized with the low-density lipoproteins derived from human sera and from saline extracts of human aortic wall. The reactions of these antisera with low density lipoproteins of serum and aorta were studied by means of the precipitin test, by double diffusion patterns in gels, and by immunoelectrophoresis. It was not possible to distinguish between the 2 antigens by any of the immunochemical procedures.

The two antisera were tagged with fluorescein nd used in an attempt to identify the location f these specific lipoproteins in a segment of a uman aorta removed during surgery for coarcta- on. No specific fluorescence could be detected the aortic sections, either in the atheromatous laque or in the vessel walls. The inability to etermine reaction sites may be due to the marked utofluorescence of the aortic wall or to an ab- nce of native lipoprotein in this preparation. urther studies using rhodamine-tagged antisera re being carried out.

:30

39. Effect of Neomycin, Para-Aminosalicylic Acid and Other Antibacterial Drugs on the Serum Cholesterol Level of Man

Paul Samuel. From the Department of Medi- ine, New York University-Bellevue Medical Center, Post-Graduate Medical School, New York, N. Y.

It was reported that the oral administration of neomycin lowered the serum cholesterol level sig- nificantly in each of 10 patients. In the present study, neomycin (Mycifradin sulfate) was given orally to 18 patients at the daily dose of 1.5 to 2 Gm. for a period varying between 4 and 20 weeks. Serum cholesterol levels were lowered significantly in each patient by the average of 17 to 29 per cent during the administration of neomycin, the over-all average being 21 per cent.

Five patients were given 60 mg. of neomycin intramuscularly daily for a period of 3 weeks. This amount is equivalent to or higher than the proportion of oral dose (3 per cent) which is absorbed from the gastrointestinal tract. The serum cholesterol level of these patients failed to show appreciable changes.

Three patients were given 6 Gm. of PAS daily by mouth for 4 weeks without significant effect on serum cholesterol levels. Subsequently, 12 Gm. of PAS was given to 2 patients for 9 and 4 weeks respectively. The average serum cholesterol level was lowered by 24 per cent in one and 26 per cent in the other patient.

Phthalysulfathiazol, isoniazid, streptomycin, oxytetracycelin, polymyxin B sulfate, bacitracin, novobiocin and carbomycin were given each orally to 2 or more patients during a period of 2 to 4 weeks. No appreciable changes were noted in serum cholesterol levels following the administra- tion of any of the above drugs.

The findings indicate that the effect of neomycin depends upon its action in the gastrointestinal tract. This might be due to the modification of he intestinal bacterial flora and/or the inhibition of intestinal enzyme systems. The mechanism of action of PAS cannot be explained at the present time.

3:45

40. Treatment of Obliterative Arterial Disease with Relaxin

Gus G. Casten and Hugh R. Gilmore, III. From the Research Department, Miami Heart Institute, and Department of Medicine, University of Miami School of Medicine, Miami, Fla.

Relaxin, a nonfeminizing hormone produced by the mammalian ovary, exerts a direct effect upon connective tissue. This material produces an increase in blood flow, evidenced by relief of Raynaud's phenomenon and healing of ischemic ulceration in scleroderma, as previously reported by this laboratory. This report is a study of 12 patients with arteriosclerosis obliterans and 2 patients with Buerger's disease treated with Relaxin during the past 2 years. All patients had advanced disease refractory to conventional therapy.

Relaxin intramuscular injections (20 mg. gelatine solution daily or 20 mg. repository solution twice weekly) were coupled with oral estrogen "priming" (Premarin 1.25 mg., 3 times weekly). Healing of ischemic ulceration has been demonstrated consistently. Clinical improvement in claudication and disappearance of rest pain has been apparent in all patients.

Surface skin temperature under conditions of maximal vasodilation was used as a measure of blood flow to the toes. The mean pretreatment skin temperature of 12 patients was 28.0 C. (normal range 31.0 $\pm$ 1 C.). Measurements at intervals of 1 month revealed a progressive rise with Relaxin therapy. After 3 months the mean level had increased to 31.0 C. ($p > 0.001$), and every patient studied showed an increase in temperature. This improvement is maintained in patients studied for over 1 year provided adequate dosage of Relaxin is given.

Relaxin presumably alters collagen and hence enhances perfusion from the arterial tree. Our experience to date indicates that this hormone will prove to be a significant advance in the therapy of obliterative arterial disease.

4:00

41. Serum Cholesterol Reduction with D-Thyroxine

Richard J. Jones. From the Department of Medicine, University of Chicago, Chicago, Ill.

Manifestly pure d-thyroxine was administered to 15 patients with clinically stable angina pectoris or a healed infarct who were euthyroid but hy-

percholesteremic. During a 6 month control period, 10 had mean serum cholesterol levels above 300 mg. per cent and the remainder above 250 mg. per cent. Oxygen consumption, pulse rate, blood pressure, and serum lipids were determined in the basal state before and after 3 months on d-thyroxine, and the serum cholesterol was followed at biweekly intervals throughout. Most patients were started on 8 mg. per day, initially, but later this was adjusted downward in some patients to 6 or 4 mg. per day.

Each of the patients showed a dramatic fall in serum cholesterol within 2 weeks, which was sustained and showed a tendency to "escape" toward control levels in only 2 cases. The mean reduction from control levels was 25 per cent. At the dosages employed, d-thyroxine was not completely free of calorigenic effects. Certain patients had an increase in BMR, lid lag, tremor, or frequency of angina during the treatment period. These effects, plus our experience in titrating d-thyroxine and l-thyroxine in 1 myxedema patient, indicate that, in large enough dose, d-thyroxine certainly does have a calorigenic effect in humans. On the other hand, a striking hypocholesteremic effect is seen, frequently with doses of only 4 to 6 mg. per day, which has been sustained for at least 3 months. With proper individualization of dose, this hypocholesteremic effect may be achieved short of undesirable side effects.

4:15

42. Effect of Nonionic Detergents on Electrophoretic Mobility and Ultracentrifugal Distribution of Human Serum Lipoproteins

T. T. Tsaltas and L. M. Tocantins. From the C. D. Cardeza Foundation, Jefferson Medical College, Philadelphia, Pa.

The admixture of 0.5-1.5 per cent Tween in the buffer used for paper electrophoresis produced marked changes in the electrophoretic mobility of serum lipoproteins, so that the α^1-lipoproteins no longer migrated with the α^1-globulin but in a position close to the origin and behind the β-lipoproteins. The same changes were produced by incubating 0.5 per cent Tween with serum at 37 C. for 1-2 hours. The identity of the altered lipoproteins bands was established by the use of isolated α^1 and β-lipoprotein. These changes were apparently produced by the strong attachment of Tween on the lipoprotein molecules as shown by studies using I^{131}-tagged Tween 80 and could not be reversed by prolonged dialysis.

Changes were also evident in the flotation patterns of lipoproteins. Serum incubated with 0.5 per cent Tween 40 for 1 hour and centrifuged in a preparative ultracentrifuge for 24 hours at 114,000 G in a medium of 1.063 density, showed 80-90 per cent of the lipoproteins accumulated in the top fraction as determined by lipid analysis. Electrophoretically such fractions contained both the α^1- and β-lipoproteins. With ultracentrifugation at densities of 1.018 and 1.006 a decrease in the amount of lipoproteins accumulated at the top fraction was observed, as compared with lipoprotein fractions of the same density but without Tween.

Studies are in progress using the analytical ultracentrifuge to determine detailed patterns of the alterations of the lipoprotein molecules as well as the in vivo effect of these detergents on the lipoprotein patterns of experimental animals.

TO BE READ BY TITLE

43. Cholesterol Depressing Effect of Fruits, Vegetables and Legumes when Substituted for Sucrose and Skim Milk in Human Diets

Joseph T. Anderson, Francisco Grande, and Ancel Keys. From the Laboratory of Physiological Hygiene, University of Minnesota, and Hastings State Hospital, Hastings, Minn.

Comparisons between populations subsisting on different diets suggests that not all of the mean differences in serum cholesterol values are accounted for by dietary fats. Accordingly, controlled experiments were carried out on men with diets differing in the proportions of carbohydrate calories supplied from various food sources. Diets IL and AL provided 13 per cent of calories from proteins and 16 per cent from fats and were identical except for 18 per cent of total calories from sucrose and milk carbohydrate in AL exchanged for equal calories in carbohydrates in fresh fruit, vegetables and legumes. Seven men subsisted on diet AL, then changed to diet IL for 6 weeks each, while 7 matched men made the reverse change. Similarly, 2 matched groups of 7 men each subsisted in crossover experiments on diets IM and AM which corresponded to IL and AL except that total fats provided 31 per cent of calories.

Serum cholesterol averages were 16 mg. per cent lower on the IL than on the AL diet and 19 mg. per cent lower on the IM than on the AM diet and these differences were highly significant statistically. Gas chromatograph analysis of the extracted mixed fats from the diets as fed indicated equally of IL vs. AL and of IM vs. AM diet in polyunsaturated fats but the IL and

I diets provided a slightly higher (+3 per nt and +1 per cent) percentage of calories om saturated fatty acids than in the compari- n AL and AM diets. These fat differences would, themselves, produce slight serum cholesterol fferences in the opposite direction to those ob- rved. It is concluded that sucrose and milk gar tend to produce higher serum cholesterol lues than equal calories of carbohydrates con- ined in fruits, vegetables and legumes.

44. Coronary Blood Flow and Metabolic Factors in Experimental Atherosclerosis

T. A. Balourdas, J. J. Spitzer, M. N. Croll, and . C. Scott. From the Institute of Cardiovascular esearch and Department of Physiology, Hahne- ann Medical College and Hospital of Philadel- hia, Pa.

Experimental Atherogensis was induced in ongrel dogs by administration of I^{131} followed y a high cholesterol diet.

The hypothyroidism induced by radioactive iodine (30-35 μc.) was shown by a marked re- duction in BMR, low PBI conversion ratio and elevated blood cholesterol level. The cholesterol diet consisted of 2.5 per cent cholesterol regime given daily for 8 to 14 months.

Fifteen experiments were performed using the nitrous oxide desaturation method for determina- tion of coronary blood flow. Observations were made on the same dogs under normal conditions, after the development of hypothyroidism and again after 8 to 14 months of cholesterol diet. Coro- nary sinus and femoral artery blood samples were analyzed for O_2, CO_2, N_2O and unesterified fatty acids (UFA).

In normal dogs average values were similar to those previously reported. The hypothyroid condi- tion showed 25-30 per cent reduction in: coro- nary sinus flow, LV O_2 concentration, heart rate, cardiac index and LV work, but increased CVR. Atropine increased: CSBF, LV O_2 concentration, mean arterial blood pressure, heart rate, cardiac index, LV work, and decreased LV efficiency and CVR.

UFA uptake by the myocardium was signifi- cantly higher in normal than in the hypothyroid. Atropine increased UFA uptake in both groups.

In the atherosclerotic dogs the CSBF, CVR, LV efficiency, LV O_2 consumption, UFA, and other factors were lower than in hypothyroid condition. Hypercholesterolemia was increased. After each terminal experiment postmortem findings showed generalized atherosclerosis of coronary and systemic arteries confirmed micro- scopically.

45. Effect of an Anion Exchange Resin on Serum Cholesterol in Man

Stanley S. Bergen, Jr., Theodore B. Van Itallie, David M. Tennent, and W. H. Sebrell. From the Medical Service, St. Luke's Hospital, and the Institute of Nutrition Sciences, Columbia University, New York, N. Y., and the Merck Institute for Therapeutic Research, Rahway, N. J.

Tennent et al. have described lowering of serum cholesterol in animals fed the chloride salt of a basic anion exchange resin. This material (MK-135) is presumed to exert its effect by se- questering bile acids.

MK-135 was administered to 26 patients for periods ranging from 2 to 34 weeks. The patients were divided into 4 clinical groups: coronary heart disease, familial hypercholesteremia, mild diabetes mellitus, and normocholesteremia. The preparation was given in 4 equal doses totalling 15 Gm. per day taken with each meal and at bedtime. Six of the subjects did not display ap- preciable cholesterol lowering until this dose was doubled. Serum total cholesterol and cholesterol ester concentrations were determined at frequent intervals by the Sperry-Schoenheimer method.

Serum total cholesterol levels were lowered by more than 10 per cent in 23 of the 26 patients. Cholesterol ester changes paralleled changes in total cholesterol. The average decrease in serum total cholesterol for all the subjects during treat- ment was 20 per cent ($p < 0.001$).

No toxic side effects were seen, however 6 patients developed some constipation while on the drug. One patient had nausea and vomiting and, with this exception, there was no weight loss or evidence of impaired digestion in any of the subjects. Six subjects who were studied for 6 weeks or longer maintained lowered values of serum total cholesterol without evidence of escape from the medication. Of the 15 patients whose cholesterol levels were followed after termination of MK-135 treatment, 8 showed a rebound to levels ranging from 4.6 to 30.6 per cent above control values. After approximately 2 weeks this "rebound" group returned to control levels.

The results indicate that, within limits, a direct relationship existed between amount of resin ingested and degree of depression of cho- lesterol levels.

46. Thyroid Hormones and Cholesterol Metabolism: Effects of Side-Chain Substitutions

Maurice M. Best and Charles H. Duncan. From the Department of Medicine, University of Louis- ville School of Medicine, Louisville, Ky.

The addition of 1 per cent cholesterol and 0.5 per cent thiouracil to the diet of the albino rat for 2 weeks resulted in an increase in liver cholesterol from 211 to 1,336 mg. per 100 Gm. and an increase in thyroid weight from 5.4 to 18.1 mg. per 100 Gm. body weight. We have previously reported (1956) that, as compared to l-thyroxin, its formic acid analog (tetraiodothyroformic acid) is more active in preventing this increase in liver cholesterol than in inhibiting the thiouracil-induced goiter.

In the present study the effects of other modifications of the side-chain of l-thyroxin and l-triiodothyronine have been similarly studied. Approximately 300 Gm. rats were employed and each analog was administered subcutaneously for 2 weeks in an amount estimated to give 80 per cent goiter inhibition.

The daily administration of .004 μM per 100 Gm. of l-thyroxin resulted in 94 per cent inhibition of goiter and mean liver cholesterol of 744 mg. per 100 Gm. Daily dose per 100 Gm., mean goiter inhibition and mean liver cholesterol resulting from administration of compounds in which the following substitutions for the l-alanine side-chain of l-thyroxin had been made were: d-alanine, .02 μM, 80 per cent, 586 mg. per 100 Gm.; formic acid, 4.0 μM, 73 per cent, 402 mg. per 100 Gm.; propionic acid, .02 μM, 100+ per cent, 732 mg. per 100 Gm.; and butyric acid, .04 μM, 100+ per cent, 862 mg. per 100 Gm.

Daily administration of .001 μM per 100 Gm. of l-triiodothyronine resulted in 100+ per cent inhibition of goiter and mean liver cholesterol of 719 mg. per 100 Gm. Compounds in which substitutions for the side-chain of l-triiodothyronine had been made gave the following results: d-alanine, .016 μM, 93 per cent, 449 mg. per 100 Gm.; formic acid, 1.32 μM, 80 per cent, 615 mg. per 100 Gm.; acetic acid, .01 μM, 50 per cent, 920 mg. per 100 Gm.; and propionic acid, .004 μM, 69 per cent, 910 mg. per 100 Gm.

Although failure to obtain identical degrees of goiter inhibition precludes exact comparison, it would appear that d-triiodothyronine and d-thyroxin possess to some extent the disproportionately greater effect on cholesterol metabolism displayed by tetraiodothyroformic acid.

47. Inhibitory Action of Dietary Factors on Experimental Atherosclerosis in Young Cockerels

Clyde T. Caldwell. From the Department of Nutrition and Metabolic Diseases, The Upjohn Company, Kalamazoo, Mich.

The protective action of dietary factors for young cockerels on atherogenic regimen has been studied. As much as 98 per cent decrease in plaque formation and 54 per cent reduction in serum cholesterol may result from treatment with a combination of certain materials.

Studies of the effect of dietary fat, protein, carbohydrate, and certain vitamins and minerals on the atherosclerotic process emphasize the interrelatedness of metabolic reactions involved. They suggest the probable value of providing in the diet for more adequate enzymatic control under atherosclerotic conditions. They indicate the importance of studying vitamins and hydrolytic products of nucleic acids, as constituents of enzyme systems, in larger than normal dosage levels.

The response of young cockerels to various mixtures of these materials has been studied in both cholesterol- and estrogen-induced atherosclerosis. The amount of each substance in the mixtures was based upon an indicated number of times the normal requirement, and in most instances that amount was held constant during the experimental period.

The atherogenic diet used in the 8 weeks cholesterol method contained 0.5 per cent cholesterol incorporated into a normal chick growing mash. Two and one-half milligrams of estradiol cyclopentylpropionate in 0.5 ml. cottonseed oil was administered intramuscularly at the beginning of the 1-week experimental period as the only atherogenic agent for the estrogen method. Results obtained by each method in the study of various combinations of these materials compare favorably. The antiatherogenic response was more pronounced for certain mixtures than for individual substances.

The data to be presented support the concept of a high degree of interrelatedness among metabolic reactions involved in atherosclerosis, and that certain dietary factors in pharmacologic amounts are able to decrease greatly the severity of the disease process in cockerels.

48. Enhanced Blood Coagulation Effects of Soaps from Hydrogenated Food Fats

Herbert L. Davis and Nora L. Davis. From the Departments of Biochemistry and of Surgery, University of Nebraska College of Medicine, Omaha, Neb.

The consumption of fats rich in saturated acids appears to be especially hazardous in terms of correlation with arteriosclerotic lesions and cardiovascular deaths. Saturated fatty acids tend to be about twice as effective in raising plasma cholesterol concentrations as equal weights of the polyunsaturated acids are in lowering them. Previous experiments showed that the ability to accelerate recalcification gel rates of citrated human plasmas rises sharply with increased chain lengths of the

turated fatty acid soaps, and is markedly lower r comparable soaps of unsaturated fatty acids. he coagulation index (maximum per cent lower- g of gel time/ millimols of soap per liter re- uired to give this value) rises from 1 for C_8 caprylate) to 160 for C_{18} (stearate). In a similar eries of plasmas, soaps of oleic, linoleic, and lino- nic acids all gave C.I. values about 8, which is he value of C_{12} (laurate). Tests on many plasmas ave shown that sodium stearate is from 6 to 20 imes as coagulant as sodium oleate.

Now corn oil, cottonseed oil, and soy bean oil ave been hydrogenated to varying lower iodine alues, and their fatty acids added as sodium soaps o human plasmas before recalcification. With cot- onseed and soy oils, hydrogenation to the com- nercial I.V. 80 value approximately doubles the coagulation index. Corn oil is less affected by such a degree of hydrogenation. All 3 oils on further saturation showed continued elevation of C.I. values.

Such findings suggest that diets rich in saturated fats or in hydrogenated fats may be more likely to produce enhanced coagulability of the blood, than would similar diets based on natural oils rich in oleic acid and the polyunsaturated fatty acids. This should be a major factor in stress episodes, tending to produce thromboembolic phenomena and consequent coronary hazards.

49. Persistent Experimental Aortic Aneurysms in Dogs

Steven G. Economou, George E. Cox, and C. Bruce Taylor. From the Departments of Surgery and Pathology, Presbyterian-St. Luke's Hospital, Chicago, Ill.

Acetrizoate (Urokon) in a 70 per cent solution was injected intramurally into the thoracic aortas of mongrel dogs which were sacrificed and studied at intervals of from 3 to 30 weeks. Gross aneurysms developed and persisted. The lack of repair was attributed to the absence of injury and stimulation of subendothelial layers since nearly all repair is achieved by proliferating subendothelial cells. To further test this thesis aneurysms were produced by dissection of 60 to 70 per cent of the outer media without injuring the inner media and subendothelial layer. Aneurysms developed immediately and persisted up to 30 weeks, the longest period of observation. Other forms of arterial injury which resulted in injury and stimulation of the subendothelial layers invariably resulted in formation of thick intimal scars. In another series of animals, one-half of each aneurysm was frozen in situ so as to injure the subendothelial layer. Profuse subendothelial scars developed at the site of the transmural freezing; the adjacent area, where no subendothelial injury had occurred, showed no evidence of repair. These findings demonstrate that the stimulus to repair of aneurysms, due to loss of medial structure, was trauma to the subendothelial layer.

50. A Physical Method for Grading Fatty Streaks in the Aorta

Douglas A. Eggen and Russell L. Holman. From the Department of Pathology, Louisiana State University School of Medicine, New Orleans, New Orleans, La.

The early lesions of human atherosclerosis, fatty streaks, have been quantitated by a photographic-photometric method applied to the intimal surface of aortas that have been stained with Sudan IV. With the aid of appropriate filters, 2 very high contrast (Kodalith) negatives are made for each aorta preparation. One negative is transparent only in those areas which are stained by Sudan IV and the other negative is transparent over the whole aorta image. A photometric measurement of the mean densities of these 2 negatives then gives a measure of the fraction of the area occupied by fatty streak.

The method is time-consuming and somewhat difficult to control because of variations in background staining. It is not recommended for the grading of large numbers of preparations but is useful in research studies. Measurements made by this method on 2 sets of human aorta which had previously been graded visually gave correlations of 0.97 and 0.92 with these visual estimates

51. Liver Function Studies in Humans with Elevated Levels of Serum Cholesterol and/or Low-Density Lipoproteins

H. Engelberg. From the Division of Laboratories, Cedars of Lebanon Hospital, Los Angeles, Calif.

The liver is fundamentally involved in various phases of fat and cholesterol metabolism. Kupffer cell phagocytosis of chylomicra has also been proposed as a possible physiologic pathway for the removal of alimentary neutral fat from the bloodstream. Accordingly, a battery of liver function tests were done in about 50 private patients without evident liver disease who had markedly elevated levels of serum cholesterol and/or low-density lipoproteins.

In approximately 10-15 per cent of the subjects there was a slight abnormality of the BSP test, varying from 8-12 per cent (normal less than 7 per cent). Evidence will be presented which sug-

gests that in some cases this finding may be secondary to the elevated lipoprotein levels. In 85-90 per cent of the group all liver function tests were normal. Thus, in the majority of individuals with hypercholesterolemia and hyperlipoproteinemia, no disturbance of liver function can be demonstrated with presently available technics.

52. Effect of Nicotinic Acid on Conjugation Pattern of Bile Acids in Man

Robert B. Failey, Jr., Earlene Brown, and M. E. Hodes. From the Indiana University School of Medicine, Indianapolis, Ind.

The oxidation of cholesterol to bile acids has been shown to be an important step in cholesterol excretion. Nicotinic acid in high dosage is effective in lowering serum cholesterol levels in man. The present report deals with work undertaken to establish a relationship between administration of nicotinic acid and bile acid excretion.

Bile was obtained from 3 patients by duodenal intubation, first while they were taking nicotinic acid in divided dosage at 2 Gm. a day, subsequently 1 to 3 days following cessation of medication. Bile acids as taurine and glycine conjugates were separated by column chromatography and individual acids determined colorimetrically and spectrophotometrically.

Following cessation of medication taurocholic/glycocholic acid ratio fell 47 and 93 per cent in 2 patients, rose 12 per cent in 1. Taurocheondeoxycholic/glycochenodeoxycholic ratio fell 52, 57, and 93 per cent. Taurodeoxycholic/glycodeoxycholic ratio fell 100 per cent in 1 patient, could not be determined in 2. No consistent reaction pattern could be shown in relationships of the individual unconjugated acids.

Conjugation of glycine with nicotinic acid and its excretion as nicotinuric acid is a probable explanation for these observations. Since animals conjugating bile acids predominantly with taurine are in general more resistant to atherosclerosis than are those conjugating with glycine, taurine conjugation induced by nicotinic acid may represent a more efficient means of cholesterol excretion.

53. Effect of Triiodothyropropionic Acid on Blood Lipids

Paul F. Flynn, Stanford Splitter, Harry Balch, and Laurance W. Kinsell. From the Institute for Metabolic Research, Highland-Alameda County Hospital, Oakland, Calif.

The effect of triiodothyropropionic acid on the blood lipid levels was studied in patients with different degrees of hyperlipemia. Causes of the elevated blood lipid values varied. Bloods were at first drawn weekly, then bimonthly. The following plasma analyses were made: Cholesterol total and esters, total phopholipids, unesterified fatty acids "freely extractable lipids," and plasma total lipids.

A number of lipid baseline values were obtained for each patient. Diets and other medication had been stable for a considerable period prior to the use of this agent.

The study was designed to determine: 1. The lipid-lowering effects of triiodothyropropionic acid on a group of 15 patients. 2. The effects of the substitution of placebos for this agent on the same group of subjects. 3. The advantages, if any of triiodothyropropionic acid over the use of dessicated thyroid as a means of lowering lipid levels.

A majority of subjects showed a highly significant drop in plasma total lipids, ester and total cholesterol, and freely extractable lipids when the agent was administered. Uniformly, phospholipids fell. Unesterified fatty acids showed a significant rise in most subjects. The placebo study is currently under way.

Over 50 per cent of the subjects at some time during the study had a pulse rate of over 110. This finding correlated with the size of the dose in the individual, but not in the group as a whole. Many of the clinical effects of dessicated thyroid were observed, and in those subjects who had radioactive iodine uptake studies, suppression of thyroid activity was found to be present. It is believed that the rise in unesterified fatty acids seen in most of these subjects may be similar to the rise in unesterified fatty acid levels seen in clinical thyrotoxicosis.

In addition to the foregoing, the comparative effects of physiologic or pharmacologic dosage of dessicated thyroid in the same patients will be reported. At the time of submission of this abstract it is not clear whether triiodothyropropionic acid has any advantage over dessicated thyroid.

54. Tissue Steam-Volatile Fatty Acids in the Albino Rat

William C. Foster. From the Laboratory of Physiology Research, Misericordia Hospital, Philadelphia, Pa.

A steam distillation apparatus has been modified for the determination of steam-volatile fatty acids (SVFA). SVFA were distilled from blood, kidney, liver, salivary glands, stomach, duodenum, skeletal muscle, and spleen of Wistar-strain albino rats, weighing between 500 and 600 Gm. and approximately 1 year of age. The animals were maintained on the Dietrich and Gambrill laboratory diet for rats which contained 5 per cent fat, ad

itum. Approximately 1 Gm. of tissue was homogized in a tissue grinder in 2 per cent zinc sulte, followed by 0.5 N sodium hydroxide. The VFA were then determined by a modification of e method of McClendon. The average rat blood VFA compared favorably with human blood reults of 0.0035 in the former and 0.003 N in the tter. The blood-heart muscle ratio was found to approximately 1:4, the blood-kidney ratio was the order of 1:6, and a high ratio of 1:8 was at of blood-liver.

55. Distribution of Atheromatous Plaques in the Aorta, Renal and Coronary Arteries

Seymour Glagov and Donald A. Rowley. From he Department of Pathology, University of Chiago, Chicago, Ill.

Regardless of etiologic factors in genesis of atherosclerosis, hemodynamic factors may affect the localization of atheromatous plaques. Studies on hemodynamic factors have usually been limited to investigation of local conditions at ostia or bifurcations, or to peculiarities of vessel contour, etc. However, hemodynamic factors may also vary in major arteries because of differences in blood flow in the tissues supplied. Because of known and presumed differences in blood flow in the myocardium and kidney, the distribution of atherosclerotic plaques was compared in the coronary and renal arteries as well as in the aorta.

The aorta, main coronary and renal arteries obtained from 200 consecutive autopsies (106 males, 94 females, ages 5 to 83) were fixed and preserved in plastic bags. The thoracic aorta, abdominal aorta, coronary and renal arteries, ranked according to the extent of atherosclerosis, were graded 0 to 4+.

In the entire series coronary atherosclerosis was 1+ or greater in 140; coronary artery atherosclerosis was greater than renal artery atherosclerosis in 137 and equivalent in 3. In no instance was renal atherosclerosis greater than coronary atherosclerosis. The findings establish beyond doubt that the renal arteries are spared or relatively spared of atherosclerosis; this is in spite of the fact that the renal arteries originate from a segment of the aorta which often has severe atherosclerosis.

A pattern of distribution, coronary>>thoracic aorta< abdominal aorta>>>renal atherosclerosis was present in specimens from 14/20 patients with diabetes, 44/60 patients with hypertension, and 7/8 patients who died of myocardial infarction. It will be shown that this pattern of distribution is also seen in many vascular trees from patients without diabetes, hypertension or myocardial infarction. Hemodynamic factors which may in part account for the selective localization of atherosclerotic plaques in these arteries will be discussed.

56. Effect of Dietary Fat and Ethanol on Serum Cholesterol Concentration

Francisco Grande, H. W. Heupel, D. S. Amatuzio, and L. J. Hay. From the Jay Phillips Research Laboratory of Mount Sinai Hospital and The University of Minnesota, Minneapolis, Minn.

Total serum cholesterol concentration was measured in groups of apparently healthy dogs subsisting on diets of different fat content, with and without administration of ethyl alcohol. A reversal, or switchback, design was adopted in all the experiments. The effect of increasing the fat content of the diet from 4 per cent of the total calories to 40 per cent (from lard) was tested in 18 dogs. The mean serum cholesterol concentration on the low fat diet was 135 ± 6.0 mg. per 100 ml., as compared with 188 ± 7.5 mg. per 100 ml. on the high fat diet. The mean difference (53 ± 7.2 mg. per 100 ml.) is highly significant ($p = 0.0001$).

Administration by stomach tube of 1.65 Gm. of ethanol per Kg. per day, resulted after 2 weeks in a mean increase of serum cholesterol of 52 ± 8.2 mg. per 100 ml., in 8 dogs subsisting on the low fat diet ($p < 0.001$). The same dose of alcohol given to 8 dogs subsisting on the high fat diet (40 per cent of total calories from lard) produced a mean increase of serum cholesterol concentration after 2 weeks of 83 ± 11.2 mg. per 100 ml. ($p = 0.0002$).

Similar results were obtained when the same amount of alcohol was given to dogs subsisting on a high fat diet (40 per cent of total calories from fat) in which sunflower oil was used in place of lard.

The serum cholesterol concentration decreased when alcohol administration was discontinued, reaching the pre-alcohol level in about 2 weeks.

Administration of 3 oz. of whiskey per day (0.45 Gm. of ethanol per Kg. per day), to 60 healthy men subsisting on a high fat diet (40 per cent of total calories from fat, approximately) for 3 weeks, failed to produce any significant change in serum cholesterol concentration.

Results of experiments in man with higher doses of alcohol (1.36 Gm. of ethanol per Kg.) will be reported.

57. Studies on Protein Component of β-Lipoprotein

Scott Grundy, A. Clark Griffin, and Harold L. Dobson. From the Departments of Medicine and Biochemistry, Baylor University College of Medicine, Houston, Tex.

Despite extensive research on the properties of serum lipoproteins, relatively little is known regarding the protein portion of these complexes. The protein moiety may be studied while combined with lipid or following removal of the lipid. From lipoproteins of various classes we have removed the lipid by extraction and studied the resulting protein portion. It would appear that the protein moiety of the very low-density lipoproteins differs from that of the medium-density and high-density lipoproteins. This would suggest that if low-density lipoproteins are converted to higher density ones a change in the protein moiety must also occur. This ability to convert very low-density lipoproteins to higher ones appears to be absent in some patients with essential hyperlipemia, and this may represent a protein defect as well as a lipid defect. Rabbits fed cholesterol appear to have the same deficiency in conversion of lipoproteins to a higher density. It has also been observed that these lipoproteins have the ability to bind further lipid substances such as cholesterol and lipid containing surface active agents.

58. Nephrosclerosis and Hypertension in the Absence of the Adrenal Gland

Dwight J. Ingle and George F. Wilgram. From the Ben May Laboratory for Cancer Research, University of Chicago, Chicago, Ill.

While the etiology of essential hypertension is obscure it has been claimed that derailment of adrenal cortical function is a principal causative factor. The supporting evidence comes from studies in which salt loaded uninephrectomized rats were overdosed with adrenal cortical hormones. In extension of an earlier study we have kept 14 male and 23 female adrenalectomized, uninephrectomized rats either on a 4 or 12 per cent salt diet without cortical hormone therapy for 6 months. Almost all experimental animals showed some degree of damaged convoluted tubules with cast-formation and early involvement of the glomeruli. Average blood-pressure rose significantly above normal. In 6 animals incipient nephrosclerosis was definitely present despite the absence of the adrenal gland. These findings are interpreted as providing preliminary evidence that high salt loads alone are capable of inducing the above mentioned pathology and that the adrenal hormones play but a permissive role in the induction and in the perpetuation of nephrosclerosis and hypertension.

59. Serum Cholesterol in Man and Complex Carbohydrates in Diet

Ancel Keys, F. Grande, and J. T. Anderson. From the Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minn., and the Hastings State Hospital, Hastings, Minn.

Populations characterized by low serum cholesterol values generally subsist on diets low in saturated fats but frequently high in vegetables and fruits that conceivably could influence the serum cholesterol. Such diets are relatively high in complex carbohydrates, particularly fiber, and pectin. To study these questions, 4 controlled experiments were made on groups of men subsisting on constant diets except for being with or without added (15 Gm. daily) cellulose fiber ("alphacel") or U.S.P. pectin for alternating 3-week periods. In each experiment, after 4 weeks of stabilization control, half the men received the supplement in the first period but not in the second while the other men (group-matched) followed the reverse order. Fourteen men on a controlled diet of the usual American type showed no effect on serum cholesterol of adding or removing fiber. Another 14 men on another diet with the same amount and kind of fat and equal content of protein and carbohydrate likewise showed no change of serum cholesterol when given fiber. Twenty-six men on a diet similar to the usual American diet but made high in total protein for another purpose showed an average fall of serum cholesterol of 9.3 mg. per cent ($p = 0.02$) when receiving pectin. On an equivalent modified form of this diet, the 26 men showed serum cholesterol averaging 10.0 mg. per cent lower when receiving pectin than without this supplement ($p < 0.001$). It is concluded that 15 Gm. of pectin has a significant cholesterol lowering effect which on these diets amounted to 5 per cent of the pre-existing level.

60. Diurnal Serum Lipid Levels of Children with Cystic Fibrosis of the Pancreas

Peter T. Kuo and Nancy N. Huang. From the Hospital of the University of Pennsylvania, Philadelphia, Pa.

A decreased fat absorption has often been demonstrated in children with cystic fibrosis of the pancreas. This naturally imposed fat restriction, which is controllable to a certain extent by pancreatic extract, offers a unique condition for the study of the effect of dietary fat upon the serum lipid concentrations.

Diurnal serum lipid variations of 9 children with cystic fibrosis of the pancreas and 7 normal controls on mixed diets supplemented with predigested proteins and carbohydrates were studied before and after the use of pancreatic extract. During each study, serum triglycerides, phospholipid and cholesterol were determined at 4 hour intervals for 24 hours.

In none of the children were any consistent diurnal serum cholesterol and phospholipid patterns observed. In both the normal and diseased groups the mean serum cholesterol concentrations were 175 and 124 mg. per cent and the phospholipid 180 and 165 mg. per cent respectively. In all 9 patients with pancreatic disease diurnal serum triglyceride curves remained flat following meals. These curves dipped slightly after midnight and rose to small peaks with prolonged fasting. Following the use of pancreatic extract, the serum triglyceride curves of 6 out of the 9 patients changed toward normal, showing significant postprandial rises and sharp dips to the respective fasting levels before breakfast. Pancreatic extract administration did not alter the serum triglyceride curves of the normal controls. Despite the chronic decrease in fat absorption, the mean fasting serum triglyceride concentrations of the patients was the same as that of the normal children.

61. Relationship between Changes in Coagulation Indices and Blood Lipids during Alimentary Lipemia

A. Little, E. A. Murphy, J. F. Mustard, and H. M. Shanoff. From the Department of Veterans Affairs, Sunnybrook Hospital, Toronto, and Department of Medicine, University of Toronto, Toronto, Canada.

Following fat ingestion, there is an increase in serum lipids and acceleration of clotting. Phospholipids and triglycerides appear to influence clotting. Therefore, the changes in these lipids and the coagulation indices were studied during alimentary lipemia in humans.

Forty-five fasting males ages 30-50 (19 coronary patients and 26 controls) were fed a breakfast rich in dairy fats and eggs. Blood samples were obtained before and 5 hours post cibos.

During alimentary lipemia, there was a significant change in serum triglyceride, phospholipid, Russell viper venom time and plasma Christmas factor activity in both groups. The whole blood clotting time (in silicone tubes) decreased significantly in the coronary group only. The serum total and free cholesterol showed little change. Significant correlations between the serum lipid changes and the changes in the coagulation indices were found only in the coronary or the combined groups and not in the control subjects.

Serum triglyceride correlated significantly with plasma Christmas factor activity changes in the combined group ($r = .44$, $p < 0.5$), while in the coronary group, the significance was borderline. Triglyceride correlated with the whole blood clotting time in the combined and coronary groups ($r = .46$ and $.54$, respectively). There was no correlation of triglyceride with Russell viper venom time.

Serum phospholipid correlated with plasma Christmas factor activity changes and only in the coronary group ($r = .47$).

It is concluded that changes in plasma Christmas factor activity may be related to changes in serum triglyceride and phospholipid following a fat meal in susceptible subjects. Changes in whole blood clotting time appear to be related to changes in triglycerides alone. Russell viper venom time appears to be unrelated to changes in serum lipids. This suggests that the various clotting tests may be influenced by different lipid fractions during alimentary lipemia.

62. Comparative Effects of Glycocyamine and Nicotinic Acid on Experimental Cholesterol Atherosis in Rabbits

Joseph M. Merrill, Jean Burkhalter, Bonnie Keith and Walter Earley. From the V.A. Hospital, Nashville, Tenn.

The major portion of administered nicotinic acid is excreted as a methylated derivative and glycocyamine is methylated to creatine. These excretory phenomena offered the possibility of investigating the comparative effects of these 2 substances on experimental cholesterol atherosis in rabbits.

In this study groups of rabbits (6 adult males per group) were fed a stock diet plus 2 per cent cholesterol; a stock diet plus 2 per cent cholesterol with 0.4 per cent glycocyamine and a stock diet plus 2 per cent cholesterol with 0.4 per cent nicotinic acid. Serum cholesterol and body weight were determined at weekly intervals. After 8 weeks of the experimental diets the animals were killed and total cholesterol of the aorta and liver of the rabbits measured.

Analysis of the data obtained revealed that the average weekly serum cholesterol was lowest in the group of animals fed the nicotinic acid. After the third week of the experimental diets, the animals fed the glycocyamine had lower serum cholesterol than did the animals fed cholesterol alone. The differences, however, are not statistically significant. The aortic and liver tissue cholesterol paralleled the changes in serum cholesterol.

Measurement of the effect of short term feeding of glycocyamine on the incorporation of sodium acetate 1-C^{14} into liver cholesterol of rats indicates that the addition of the glycocyamine to the diet of the rat is associated with a twofold increase in incorporation of labeled carbon into liver cholesterol.

The results of this study suggest that nicotinic acid was more effective in preventing the anticipated rise in serum and aortic tissue cholesterol than was a similar amount of glycocyamine.

63. Hormonal Factors in the Partition of Lipoprotein Cholesterol in Healthy Subjects

Campbell Moses and T. S. Danowski. From the Addison H. Gibson Laboratory and the Renziehausen Department of Research Medicine of the University of Pittsburgh School of Medicine, Pittsburgh, Pa.

After control variations in the partition of cholesterol, lipid phosphorus and triglyceride in the serum α- and β-lipoprotein fractions were determined in 84 healthy, institutionalized men, varying doses of desiccated thyroid, triiodothyronine, triiodothyropropionic acid, and tetraiodothyropropionic acid were given for periods up to 18 months. Twelve subjects receiving 2 mg. of triiodothyronine for 99 days had a fall in mean total cholesterol from 225 to 200 mg. per cent. This decrease was maintained and was largely due to a fall in the β-lipoprotein fraction. A similarly persistent but even greater fall in β-lipoprotein cholesterol was noted with 4 mg. of triiodothyropropionic acid. Ten men receiving tetraiodothyropropionic acid for 82 days failed to demonstrate any decrease in β-lipoprotein cholesterol. The hypocholesterolemic response to varying doses of desiccated thyroid indicated that many individuals without overt evidence of thyroid deficiency will develop sharp falls in β-lipoprotein cholesterol when they receive adequate replacement doses of desiccated thyroid. Data will also be presented upon the effect of the administration of other hormones with and without thyroid upon lipoprotein cholesterol. The significance of the interrelationships demonstrated by these studies in the development of atherosclerosis and aging will be discussed.

64. Modification of Experimental Atheromatosis by a Folic Acid Antagonist

Carl Muschenheim, Seymour Advocate, and Donald W. Hoskins. From the Department of Medicine, the New York Hospital—Cornell Medical Center, New York, N. Y.

It has been observed that atherosclerosis is often mild or absent in human cases of pernicious anemia. A program has therefore been undertaken to investigate a possible relationship between vitamin B_{12} or folic acid metabolism to atherogenesis.

For the initial experiments aminopterin was selected as a readily available and easily administered folic acid antagonist. This drug, administered in the dose of 10 mg. per day subcutaneously to rabbits weighing 2-3 Kg., produces a profound and sometimes fatal anemia, but if a 2 day rest period is given each week the anemia may be maintained at an hematocrit level of 25-30 and the animals appear healthy and gain weight.

Rabbits pretreated with aminopterin for 4 weeks were fed an atherogenic diet for 8 weeks, during which aminopterin injections also were continued. The atherogenic diet consisted of a stock diet with 3/4 per cent cholesterol added. As a result of some manipulation of the aminopterin dosage during the period before cholesterol feeding was begun some of the aminopterin treated animals lost weight from overdosage and 7 of the original 20 died. The surviving animals upon reduction of dosage made good weight gains, comparable to the controls, during the cholesterol feeding period. When sacrificed after 8 weeks of cholesterol feeding the control animals, 21 in number, all had grossly demonstrable 1+ to 3+ atheromatosis of the aorta. Of the 13 surviving aminopterin treated animals 9 had no atheromatosis or doubtful deposits of minimal extent. Only 4 had definite atheromatosis comparable in extent to the controls. Serum cholesterol levels averaged 40 to 50 per cent lower in the treated animals than in the controls.

65. Comparative Incorporation of C^{14} from Labeled Acetate into Free Cholesterol, Fatty Acids and Esterified Cholesterol and Fatty Acids in the Calf Aorta

W. R. Nelson. From the Southwest Foundation for Research and Education, San Antonio, Tex.

In humans, with advancing age, and in rabbits, with induced atherosclerosis, cholesterol esters showed a greater increase in concentration than did other lipids in a study to be published. Simultaneously, but as separate entities, incorporation of C^{14} from labeled acetate into the (a) free cholesterol, (b) some representative free fatty acids, and (c) the cholesterol and fatty acids comprising the cholesterol esters have been investigated to study this matter further.

Since the calf aorta actively synthesize both fatty acids and cholesterol it was chosen as the subject for 2 perfusion experiments employing whole blood as perfusate. Perfusion A was run for 8 hours. Perfusion B was also run for 8 hours with labeled acetate in the perfusate but then a second "unlabeled" perfusate was substituted for 24 hours.

The cholesterol esters of A and B were combined after silicic acid columning. This was necessary since from both aortas a total of only 825 γ

cholesterol in the esterified form was obtained. he combined cholesterol esters were subjected to chromatographic purifications. Since 20 mg. of ee cholesterol were present in each aorta it was ot requisite to combine these fractions.

The representative free fatty acid pool was obained from the saponifiable fraction accompanyng the free cholesterol. This fraction is free of iglyceerides and phospholipids.

The results of the study indicate a five to eightold greater degree of C^{14} incorporation from abeled acetate into free cholesterol and free fatty cids than in the cholesterol and fatty acids that omprise the cholesterol esters. The significance of his finding in the light of the earlier study will e discussed.

66. Butter, Corn Oil and Fibrinolysis in Rats

Robert M. O'Neal, Roosevelt L. Tillman and Wilbur A. Thomas. From the Department of Pathology, Washington University School of Medicine, St. Louis, Mo.

The production of coronary arterial thrombi and myocardial infarcts in rats on a high-fat diet including thiouracil (0.3 per cent), sodium cholate (2.0 per cent), butter (40 per cent), and cholesterol (5 per cent), has been reported previously. In the present experiment 3 groups of Wistar rats (19 rats in each group) were established in order to determine whether or not feeding the thrombogenic diet caused interference with streptokinase-activated fibrinolysis. The "butter" group was fed the above diet, the "corn oil" group was fed an identical diet except that corn oil was substituted for butter, and the "normal" group was fed a semi-synthetic diet similar to the others but without thiouracil, sodium cholate or cholesterol and with the only added fat being 2 per cent corn oil. Three rats, 1 from each group, were bled in sequence at 12 to 40 days and fibrinolysis tested on the citrated, recalcified plasmas after the addition of lyophylized human plasma (Warner-Chilcott's Diagnostic Plasma) and streptokinase (Lederle's Varidase) solution in equal amounts to the three plasmas. The tests were performed with a "thrombelastograph."

The mean time necessary for complete clot-lysis was the same in the normal group and the corn oil group (28 minutes) but was significantly ($p < 0.05$) longer (76 minutes) in the butter group (the statistical method used was the analysis of variance of a randomized block).

These results suggest that the thrombogenic effect of the diet we have used in rats to produce coronary arterial thrombi and myocardial infarction is related to its inhibition of fibrinolysis.

67. Experiences with in vivo Production of Fibrinolysin Following Parenteral Administration of Nicotinic Acid in Humans

William B. Parsons, Jr. From the Department of Internal Medicine, Jackson Clinic and Foundation, Madison, Wis.

Intravenous injection of nicotinic acid (100 mg. in 5 minutes) in humans results in fibrinolytic activity in some instances, as demonstrated by observation of recalcified whole blood or plasma or by thrombelastographic tracings. Complete lysis of clots occurs in blood samples drawn as soon as 3 minutes or as long as 30 minutes after completion of the injection, but lesser degrees of lysis can sometimes be found in later specimens by observing tubes containing clots for 72 hours or by recording thrombelastograms for 16 to 24 hours.

The phenomenon is inhibited in patients who have been taking 3 Gm. or more of nicotinic acid daily for hypercholesterolemia. It is also inhibited for several hours after injection of nicotinic acid, failing to occur after a second injection. The frequency with which injections can be administered and consistently produce fibrinolysis has not yet been determined, and it is possible that daily or twice daily administration will result in failure to elicit this phenomenon in most patients.

Intramuscular injection of nicotinic acid (100 mg.) causes fibrinolysis in some patients but less consistently than intravenous administration. The effect of sublingual administration is currently being studied.

Nicotinamide injected parenterally fails to produce fibrinolytic effect, but its injection can inhibit the phenomenon when nicotinic acid is injected several hours later. Whether nicotinamide in multiple vitamin products taken days prior to testing can cause inhibition is uncertain. It is possible that patients receiving anticoagulants to reduce prothrombin concentration are less likely than others to develop fibrinolytic activity from nicotinic acid.

Addition of nicotinic acid to blood in vitro fails to result in fibrinolysis, regardless of whether it is added before or after coagulation occurs. Nicotinic acid blood levels, determined by bioassay, have thus far failed to show any consistent correlation with presence or absence of fibrinolysis in vivo following parenteral injection.

68. Validity of Serum Cholesterol Determinations on Postmortem Blood

J. C. Paterson and Lucy Dyer. From the Clinical Investigation Unit of Westminster Hospital, and the Collip Medical Research Laboratory, University of Western Ontario, London, Canada.

Landé and Sperry compared the postmortem level of serum cholesterol with the amount of lipid extracted from the aorta in a large series of individuals who died suddenly and violently. No significant relationship was thus obtained, but the validity of this result has been questioned because of the doubtful accuracy of cholesterol determinations on postmortem blood. We have examined this latter point during the past year.

Serum cholesterol determinations have been made serially during the last 5 years of life on 800 patients who are permanently confined to our hospital. Twenty-seven of these died during 1958-59, and on each we did an additional determination of the postmortem serum cholesterol level. The postmortem level was then compared with the mean antemortem level, with the pathologic findings, and with the clinical picture during the terminal illness.

In 20 cases the terminal illness was protracted and in these there were striking decreases (average 49 per cent) in the postmortem serum cholesterol levels compared with the antemortem levels. However, an entirely different result was obtained in persons who died suddenly and unexpectedly. In 6 out of 7 such cases, the postmortem levels were in the same range (2 per cent) as the mean antemortem levels. There was only 1 exception to this general rule: a 73-year-old man in apparent good physical health who died suddenly and unexpectedly. Postmortem examination revealed rupture of the heart through a recent myocardial infaret estimated to be about 10 days old. The average antemortem serum cholesterol in this case was 190 mg. per cent, and the postmortem level 134 mg. per cent. This case illustrates the complete unreliability of serum cholesterol levels determined during the acute stage of myocardial infarction.

In general, the results in this small series tend to support the claims of Landé and Sperry that postmortem serum cholesterol determinations are valid providing that death is sudden and unexpected and that no significant occult disease is revealed at autopsy. The corollary is that their 1936 report deserves more consideration than it has apparently received in the past.

69. Morphologic Changes in Atherosclerotic Plaques due to Exogenous Insulin Administration

Ruth Pick, and Louis N. Katz. From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

It has been established that insulin inhibits diet-induced regression of coronary atherosclerosis in chicks. Recent experiments have demonstrated that insulin also counteracts the accelerated regression of lesions seen in estrogen-treated birds. The mechanism by which insulin operates is not known. However, histologic examination revealed significant alterations of the plaques in birds exposed to insulin. Eleven per cent of the insulin-treated animals and 47 per cent of insulin plus estrogen treated animals showed an abundance of birefringent cholesterol crystals with only a very small amount of sudanophilic fat. This was not seen in control birds. Regular mash diet alone or regular mash plus estrogens in no instance produced this morphologic appearance. Ordinarily, the plaques induced during five weeks contain large amounts of sudanophilic fat with few, if any, cholesterol crystals. Evidently, insulin and/or insulin in combination with estrogen changes the character of the lipid deposit within the preexisting lesions. The significance of this phenomenon in relation to retardation of regression is not known.

70. Effects of Estradiol-17α in Males with Coronary Heart Disease

Roger W. Robinson, Norio Higano, and William D. Cohen. From the Research Laboratory and Medical Division, The Memorial Hospital, Worcester, Mass.

It was of interest to study the possible lipid-shifting effects of estradiol-17α, in view of its relative lack of estrogenicity in standard bioassays. Ten middleaged men with coronary heart disease were studied before and during oral administration of 10 mg. of estradiol-17α (AY-55102, Ayerst Laboratories) daily for 6 months. The following serum lipid parameters were checked monthly: total cholesterol, phospholipids, cholesterol/phospholipid ratio, α- and β-lipoprotein cholesterol by preparative ultracentrifugation, and the β-/α-ratio. Clinical evaluation was obtained frequently to determine the development of the characteristic effects of estrogens in males. One patient developed marked decrease of libido after 2 months of administration despite an increase of the β-/α-ratio from 5.6 to 7.5, an effect opposite to that typical of estrogens. Another patient complained of breast tenderness after 3 months, although the serum lipids remained at control levels. Of the remaining 8 men who completed the 6 months, 5 were free of estrogenic effects, while 3 developed late breast changes, one, breast hypertrophy and two, only breast tenderness. Monthly serum lipid determinations during this 6-month period showed no significant changes from control levels, whether or not estrogenic side-effects developed. Thus, estradiol-17α, while weakly estrogenic, proved to be devoid of any lipid-shifting properties at this dosage.

71. Human Pulse Rate during 24 Hours of Usual Activity

Donald A. Rowley, Seymour Glagov, and Peter toner. From the Department of Pathology, Uni- ersity of Chicago, Chicago, Ill.

Hemodynamic factors may account for the fre- uent localization of atheromatous plaques in the oronary arteries and the sparing of the renal ar- eries. Resistance to blood flow in the kidney is ow; about 25 per cent of the cardiac output flows hrough the relatively small main renal arteries. Resistance to blood flow in the myocardium in- reases during systole; thus the main coronary rteries are unique in that they supply a tissue which increases resistance to blood flow during a portion of each cardiac cycle. According to Lap- lace's law, vessel wall tension is higher in the coro- nary artery than in the renal artery during each systole. The duration of systole remains constant at about 0.25 second within the range of normal pulse rates. With a low pulse rate increased coro- nary artery wall tension during systole may not be significant but with a sustained high pulse rate increased wall tension might account in part for the localization of atherosclerotic plaques in the coronary arteries.

A pulse rate for 24 hours, integrating the varia- tions in minute rate produced by activity etc., might give useful information relating pulse rate to pathologic processes. An instrument for measur- ing 24 hr. pulse rates should be small, rugged, un- encumbering, and self-contained. In cooperation with Illinois Bell Telephone engineers we have built an instrument measuring 9 × 7 × 1.5 cm. and weighing 110 Gm. The electrical signal of each myocardial contraction, picked up from precordial electrodes and amplified, drives a cumulative counter. Electrodes which give an undistorted sig- nal regardless of body position, physical activity, or trauma to the electrodes have been designed. The electrodes are easily applied and non irritat- ing; they will not detach during strenuous exer- cise. The pulse counter is highly accurate during many kinds of activity. Preliminary data on 24 hour pulse rates will be discussed. The design of components of the counter will be presented.

72. Correlation of Activity Changes in Blood Coagulation Factors with Human Arteriosclerosis

Alfred C. Schram and L. O. Pilgeram. From the Arteriosclerosis Research Laboratory, St. Barnabas Hospital Research Foundation in cooperation with the Department of Physiology, University of Minnesota School of Medicine, Minneapolis, Minn.

A survey of the literature will reveal that information on whether blood coagulation factors change with the development of human arteriosclerosis is inadequate. The possible role of these factors in the etiology of arteriosclerosis and thrombosis points to the need for information on which factors change, if any.

A study was therefore undertaken of the changes which occur in coagulation factors with presence of human arteriosclerosis. All subjects fasted overnight for 8 or more hours. All factors were measured in the same sample of plasma from a given subject. Donors were divided into 2 groups: group A consisted of apparently healthy, young individuals (age range 22 to 28 years), while group B consisted of patients who had sustained a proven myocardial infarction at least 6 months prior to the blood drawing, and were without anticoagulant therapy for at least 5 months prior to the blood drawing (age range 36 to 74 years).

The citrated plasmas were analyzed for prothrombin; total antithrombin activity; antithrombins II and III; "stable component" (proconvertin); "labile component" (accelerator globulin); thromboplastin generation; antithromboplastic activity; fibrinogen; profibrinolysin; fibrinolytic and antifibrinolytic activities. The methods used were adapted from reported technics. Reagents were prepared only from normal human plasma and tissue, except in the case of stable component determinations, in which bovine proconvertin-free plasma was used. Test conditions were kept constant throughout the study.

The deviations of any single component within a group were large. Deviations ranged from 8 to 40 per cent from the mean for the group. However, the averages in both groups pointed to a definite increase in plasma clottability in the case of group B. Most significant were the increases in prothrombin level (34 per cent; $p = 0.03$); in thromboplastin generation (28 per cent; $p < 0.001$); and in fibrinogen level (34 per cent; $p = 0.01$). An appreciable increase in antithrombin II (19 per cent; $p = 0.06$) and in antithrombin III (33 per cent; $p < 0.002$) was also recorded. There was a trend for increased levels of stable component (14 per cent; $p = 0.25$); of labile component (38 per cent; $p = 0.25$); and of antithromboplastin (33 per cent; $p = 0.16$). In the same group, there was a slight trend for decreased values (about 10 per cent) in the levels of profibrinolysin, fibrinolysin and antifibrinolysin ($p = 0.12$).

73. Myocardial Necrosis Following Pitressin Administration in Dogs with Coronary Atheromatosis

Harry Sobel and Carl Mondon. From the Institute for Medical Research, Cedars of Lebanon Hospital, and the Department of Biochemistry &

Nutrition, University of Southern California, Los Angeles, Calif.

The role of stress and emotionality as cofactors in the genesis of hypercholesterolemia, atheromatosis, atherosclerosis and myocardial and cerebral necrosis is under investigation in this laboratory. A reasonable hypothesis in regard to cardiac angina and necrosis would be that when coronary flow is already diminished because of atherosclerosis, further impairment resulting from mechanisms engendered by stress and emotionality would impede flow to such an extent as to cause hypoxic phenomena. A study was therefore undertaken of the effect of humoral agents which are known to be released following stress, upon dogs which had been maintained on an atherogenic regimen for periods up to 1 year. Two of 9 dogs receiving 0.3 units of commercial pitressin per Kg. body weight intravenously over a period of 20 seconds died within a few minutes. Those which survived received 2 additional injections and although electrocardiographic evidence of hypoxia was present in some, there were no further deaths. The 2 dogs which died exhibited severe coronary involvement while the 7 which survived had moderate or minimal coronary atheromatosis. One of the dogs which died had previously received numerous intravenous injections of norepinephrine (30 μg./Kg.) without permanent effect. There were no deaths in 10 normal dogs receiving these agents.

These preliminary findings suggest that the dog with experimental atheromatosis may be a useful tool for study of mechanisms which are activated by stress and emotionality and which may cause myocardial necrosis. Further studies with smaller doses of pitressin and other agents should be undertaken.

74. High Incidence of Myocardial Infarcts in Ulcer Patients Treated with Sippy and Other High-Milk Diets: A Study of Autopsied Patients in Fifteen Hospitals

Wilbur A. Thomas, Robert M. O'Neal, Richard D. Briggs, Martin L. Rubenberg, and W. Stanley Hartroft. From the Department of Pathology, Washington University School of Medicine, St. Louis, Mo.

In order to evaluate the role of milk products in the production of the high incidence of myocardial infarcts in patients with peptic ulcers, the incidence of myocardial infarcts has been determined for 3 groups of autopsied patients matched for age, sex, race, place, and period of death. The 3 groups of patients from 10 medical centers in the U.S.A. and 5 in Great Britain, are as follows: (1) Patients with peptic ulcers who had a history of treatment with the Sippy or other high-milk diet (Sippy-ulcer), (2) patients with peptic ulcers who were not known to have been so treated (non-Sippy-ulcer), and (3) nonulcer patients matched as indicated above with the other 2 groups. Statistically significant differences were found between the incidences of myocardial infarcts in the Sippy-ulcer patients and the incidences in either of the other 2 groups. These differences were apparent in patients from the hospitals in the U.S.A. as well as those from Great Britain.

In the U.S.A. the incidence of myocardial infarcts in 97 Sippy-ulcer patients was 36 per cent compared to 15 per cent in the other 2 groups ($p = 0.01$). In Great Britain, the incidences in 95 Sippy-ulcer patients was 48 per cent, 3 per cent greater than the incidence in the non-Sippy-ulcer ($p = 0.01$) and the 8 per cent incidence in the nonulcer patients ($p = 0.05$). No significant differences were present between incidences of myocardial infarcts in the non-Sippy-ulcer and nonulcer patients.

This relationship between the therapeutic dietary regimen and the incidence of infarction is beyond any statistical doubt, but these data only indicate a strong association between the 2; further studies would be necessary to establish any cause and effect basis.

75. Early Lesions in Rat Atherosclerosis

Bernard C. Wexler, George W. Kittinger, and Benjamin F. Miller. From the May Institute for Medical Research of the Jewish Hospital of Cincinnati and the Departments of Pathology and Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio.

Rats, bred repeatedly, developed arteriosclerosis spontaneously. The incidence and severity of these lesions may be increased by unilateral nephrectomy and injection of ACTH. Adrenal steroid analyses, adrenal histology, and thymic involution suggest participation of the pituitary-adrenal axis in the pathogenesis of the arterial damage. Lipids, demonstrable by the usual histological technics, did not appear except in the more advanced lesions; serum cholesterol levels remained essentially normal.

An attempt was made to locate and describe the earliest changes. Female and male rats (Sprague-Dawley), on a regular diet, were bred repeatedly and some sacrificed after each breeding. Other breeders were subjected to unilateral nephrectomy, treated with ACTH, or a combination of ACTH and nephrectomy. The earliest change observed was a subintimal accumulation of acid mucopoly-

ccharide (AMP) followed by fibrosis. Medial astic fibers became swollen and were surrounded AMP-positive granules. Next there appeared astosis and pooling of mucopolysaccharides. In ore advanced lesions, sites of dystrophic calcifica-on were accompanied by lipid infiltration. Males nd females differed in the morphologic develop-ent of atherosclerosis. Grossly detectable plaques ppear in females by the fourth breeding, but not the males.

ACTH and nephrectomy accelerated the arterio-lerosing process and produced unusual accumu-tion of mucopolysaccharides and heavy subinti-al fibrosis. The aorta appears to be the primary target organ," i.e., lesions appear first in the aorta nd only secondarily in other organs.

76. Comparative Actions of Female and Male Sex Hormones on Aortic Atherosclerosis of Cockerels Fed a Cholesterol-Sugar Diet

Harry Y. C. Wong, Frank B. Johnson, Beatrice Liu and Rose Shim. From the Department of Physiology, Howard University Medical School, and the Armed Forces Institute of Pathology, Washington, D. C.

It has been reported that administration of estrogen to cholesterol fed chicks could reverse coronary atherosclerosis, but it had no significant effect on the aorta. Previous reports from our laboratory have shown that exercise and administration of male sex hormones to cockerels or capons significantly reduced blood cholesterol and aortic and coronary atherosclerosis in birds fed a diet of 2 per cent cholesterol and 5 per cent cottonseed oil. The present investigation was undertaken to study the effects of male and female sex hormones in reversing atherosclerosis of cockerels fed a diet of 2 per cent cholesterol and 5 per cent cottonseed oil. At the end of 10 weeks on this diet, 20 cockerels were sacrificed to determine the degree of aortic atherosclerosis. Hardly any atherosclerosis was seen, although there was a very significant increase in the blood cholesterol. Subsequently, cockerels were placed on a diet of 2 per cent cholesterol, 5 per cent cottonseed oil and 30 per cent sugar. Three groups of 10-week-old cockerels were used: Group 1, cockerels fed a 2 per cent cholesterol and 5 per cent cottonseed oil diet supplemented with 30 per cent sugar; group 2, similarly treated as group 1 except they were treated with 1.25 mg. testosterone propionate; and group 3, birds on a similar diet as group 1 except these were injected with 1.0 mg. of estradiol benzoate. After 7 weeks of treatment, it was observed that group 2 had the lowest blood cholesterol, and group 3 had a higher level than group 1 or 2. Upon autopsy, the testosterone-treated group had the least aortic atherosclerosis. This was statistically significant when compared to groups 1 and 3. Gross grading of the aortas of group 3 was higher than that of the controls.

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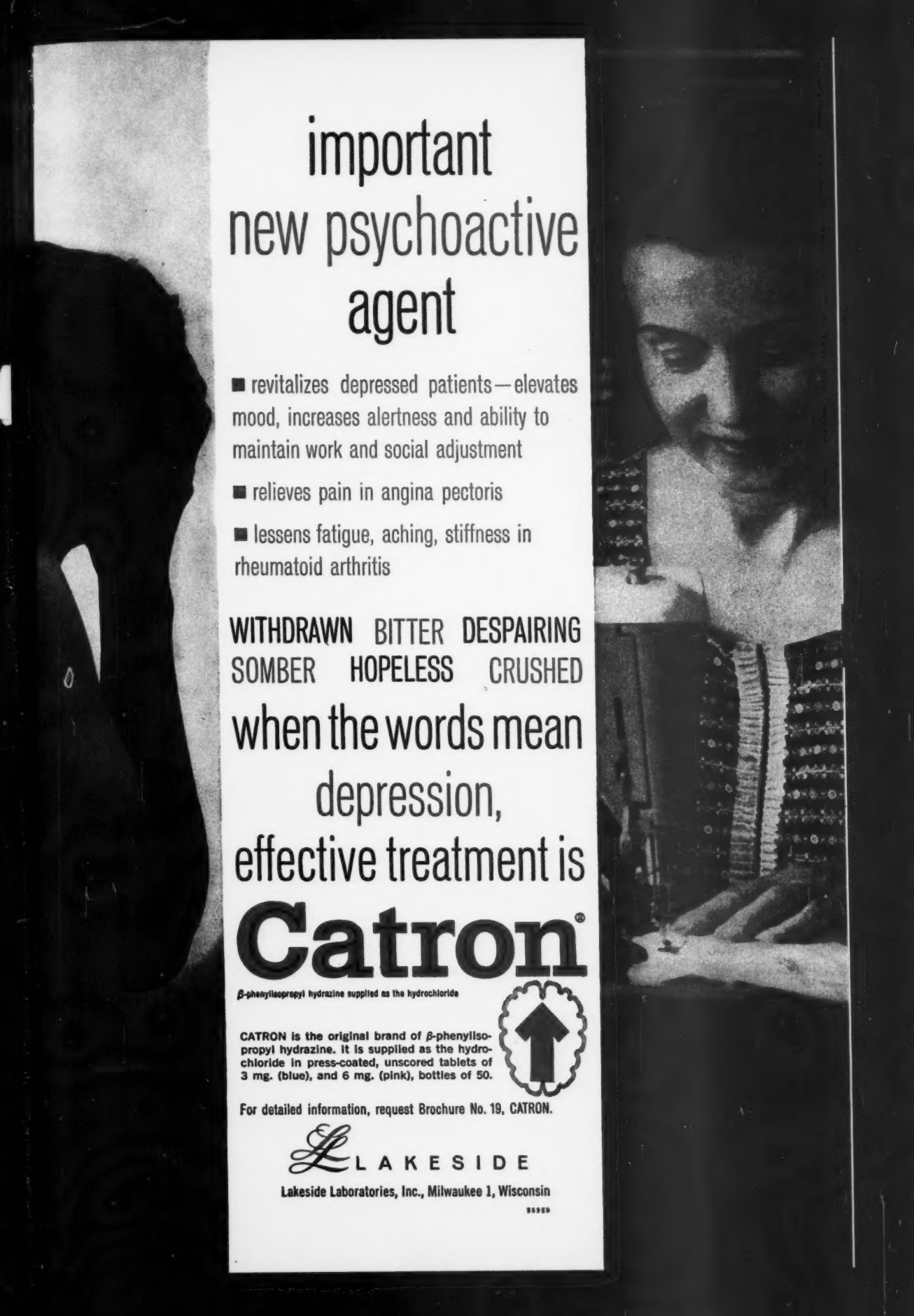

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